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MUSCULAR CONTRACTION

AND THE REFLEX CONTROL OF MOVEMENT

By

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B.Sc. (Harvard): M.A., Ph.D. (Oxon)

BALTIMORE
THE WILLIAMS & WILKINS COMPANY
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TO

CHARLES SCOTT SHERRINGTON

PREFACE

The present monograph is concerned primarily with the activity of skeletal muscle: its mode of contraction and the nature of its reflex control. The scope of the book might be broadly expressed by Aristotle's designation, *De Motu Animalium,* for I have attempted to study muscle as a means of motion rather than as a machine for transforming energy. This has entailed consideration of both the peripheral and the reflex aspects of the physiology of muscle,—subjects which in the past have been sharply separated. Being convinced, however, that such a separation is artificial, I am emboldened to present these two aspects of physiology within the compass of a single volume. The first part of the monograph deals with the phenomena associated with contraction of the individual muscle fibre, and the second with the way in which individual fibre-responses are summated by the central nervous system into the delicately adjusted and often long-sustained postures characteristic of living organisms. Attention is thus focussed throughout upon the muscle and its constituent fibres. Without a comprehensive knowledge of their behaviour, one is hindered in an analysis of reflex processes.

Full description is given, moreover, of the recent advances in the physiology of muscle and of central nervous processes which have been made possible through the introduction of more accurate recording methods, especially the new technique of the torsion-wire myograph devised by Professor Sherrington. The use of this instrument in conjunction with the string galvanometer has considerably increased the value of either form of record taken independently, and has cast new light upon the relation between electrical and mechanical activity of muscle. A description of these instruments, and of the method employed for obtaining simultaneous mechanical and electrical records by means of them, is given in the Appendix.

The experimental observations, upon which rest the chief conclusions of Part I, were made by me upon intact muscle (active circulation) under physiological conditions closely approaching the normal. When evidence is drawn from other authors, it has been done only after a careful study of their writings, or after having either seen or repeated their experiments. The conclusions and inferences are therefore based almost wholly upon first-

hand information. This is my excuse for a somewhat arbitrary choice of subject matter. Moreover, " I have been particular to set forth evidence upon evidence for a given conclusion in the book, feeling that no doctrine is sufficiently supported if yet another serious argument may be urged in its favour."[1]

In dealing with controversial subjects I have tried to be guided by Goethe's dictum: "Je ne juge pas, je raconte."[2] If unwittingly I have been unfair or inaccurate in presenting the evidence of another investigator, I take this opportunity of expressing my sincere regret and of offering my apology. In no existing field of knowledge, perhaps, is the Hippocratic adage, "experimentia fallax, judicium difficile," more true than in physiology of animal movement. In discussing many questions, it is only possible to describe experiments and to record results. When two or more theories exist to account for the same body of experimental observations, I have deemed it proper, after examining both explanations, to state my personal preference with reasons.

A brief historical sketch of the physiology of muscle has been given in the Introduction. The study of the early period from Aristotle to von Haller has proved to be exceptionally interesting, since it shows in an unusual way the continuity of ideas in a relatively limited field of human thought. Naturally, full details cannot be given in a brief introduction, but it is my purpose to prepare at a later date a more extensive history of the early contributions to muscle physiology. The history of neurophysiology and neurology, on the other hand, has been written by others, and no phase of science, it seems to me, has ever been more fortunate in its historians. For those interested, it is sufficient to direct attention to the work of Max Neuberger[3] and that of Jules Soury.[4] A most useful brief history of neurology has recently appeared by Dr. Fielding Garrison as an introduction to the tenth edition of Dana's *Text-book of Nervous Diseases* (New York: Wm. Wood, 1925).

The chapters on the knee-jerk, muscle tonus, the stretch reflex, the central inhibitory process, the coördination of antagonistic muscles, and the functions of the cerebellum are presented in the form of short essays which

[1] Lewis, *The Mechanism and Graphic Registration of the Heart Beat*, Preface, p. v.

[2] Goethe, *Sur la discussion academique entre Cuvier et Geoffroy Saint-Hilaire.* See Isidore Geoffroy Saint-Hilaire's "Life" of his father (Paris, 1847).

[3] *Die historische Entwicklung der experimentellen Gehirn-und Rückenmarks-physiologie vor Flourens*, Stuttgart, 1897.

[4] *Le systeme nerveux central, structure et fonctions, histoire critique des theories et des doctrines*, 2 vols., Paris, 1899.

can be read independently of the rest of the volume. The appended bibliography will be, it is hoped, a useful guide to early, as well as to recent work.

My pleasantest duty is to acknowledge the great debt of gratitude which I owe to my teachers, colleagues, and many friends who have assisted me in the preparation for and of this work. Of my teachers, I am most indebted to Sir Charles Scott Sherrington. His judgment has been my guide, his friendship and encouragement my inspiration.

I am also particularly indebted to my former teacher, Dr. Edward L. Mark, for most generous assistance in the revision of the manuscript. It is a pleasure to record my obligation to Professor and Madame Lapicque,—and many friends in their laboratory at the Sorbonne,—whose gracious hospitality and helpful guidance has been much appreciated. To my collaborator and friend, E. G. T. Liddell, I am also indebted in countless ways. His exceptional operative skill has made possible a degree of accuracy and success, in our joint investigations, which could never otherwise have been attained, and in addition this work has benefited throughout by his judicious criticism. I wish also to mention those in America and elsewhere who have been kind enough to peruse various chapters of this monograph and to give me the benefit of their valued criticism, especially Drs. E. D. Adrian, David Brunswick, McKeen Cattell, Stanley Cobb, Hallowell Davis, Derek Denny-Brown, Alexander Forbes, Herbert Gasser, Grayson McCouch, Frederick Miller, Frederick H. Pratt, Alfred Redfield, and Henry Viets.

I am under obligation to the President and Fellows of Magdalen College for encouraging the experimental research upon which this work is largely based, especially for making possible the purchase of the string galvanometer. Grateful acknowledgments are also due to Miss F. Buchanan, who generously placed at my disposal her powerful arc lamp and other useful accessories; to the Christopher Welch Trustees, who have defrayed the considerable expense of photographic plates and other incidentals; to the Royal Society for furnishing me with excellent electrotypes of illustrations published in their Proceedings; to Mr. C. J. O'Neill (Oxford) who made the camera, the myograph, and the stimulating and signalling keys; and finally to Mr. George Cox (Oxford) whose skilled assistance in making mammalian preparations was most valuable.

Thanks are also due to many fellow-workers and editors for permission to use their figures. Due acknowledgment will be found in each case in the letter-press of the figure.

J. F. Fulton.

The Harvard Medical School.
July 1926.

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PART I

The Nature of the Contractile Response of Individual Skeletal Muscle Fibres

"But what I have said of Haller justifies, I venture to think, the assertion that we have gone forward so much because we have laboured on Haller's lines. He expounded the nervous system in a spirit which has become the modern spirit, and our progress has been due to our following his example. And if he with the knowledge and the means at his command seems to us to-day often to have walked haltingly or even often to have gone astray, we may ask ourselves this question: Are not we, with all the knowledge and the means at our command, walking also haltingly, if not more haltingly; and are we not as often, if not more often, going astray? Shall we not seem so to those who tell our story a hundred years to come? For indeed it is one of the lessons of the history of science that each age steps on the shoulders of the ages which have gone before. The value of each age is not its own, but is in part, in large part, a debt to its forerunners. And this age of ours if, like its predecessors, it can boast of something of which it is proud, would, could it read the future, doubtless find also much of which it would be ashamed." (Sir Michael Foster, *History of Physiology*, p. 297.)

HISTORICAL INTRODUCTION

Muscle, as a word in the English language, has a somewhat curious derivation. On referring to *Murray's New English Dictionary* (Oxford), one finds that it is diminutive of the Latin *mus, i.e., musculus*, meaning a small mouse. The ancients likened the shape of the fleshy parts of their bodies to mice, and in this way the word muscle appears to have had its origin.

The history of the physiology of nerve and muscle may be divided somewhat arbitrarily into four phases: the period of the forerunners, beginning with the Greeks and the Romans and ending with Whytt (1714–1766) and von Haller (1708–1777), the rise of electrophysiology originating with Galvani (1791) and continuing to the present day, the development of muscular thermodynamics and chemistry, which commenced with von Helmholtz (1847) and has culminated in the outstanding discoveries of Hill and Meyerhof, and finally, the growth of the "all-or-none" theory, which arose in the observations of Bowditch and Kronecker, and led up recently to the important contributions of Pratt. It will be convenient to consider each phase separately.

THE FORERUNNERS

In tracing the development of the physiology of muscle, one naturally turns first to the Greek physicians and philosophers, for, broadly speaking, "nothing moves in the world that is not Greek in origin" (Sir Henry Maine). First let us examine the views of Aristotle (384–322 B.C.). One who expects to find in Aristotle anything in the nature of biological experiment will, of course, be disappointed. His contribution was of another sort. In the *De Motu Animalium* and the *De Incessu Animalium*[1] one finds rather the warm sunshine of the logical analysis which has distinguished Aristotle in so many fields of human thought. As a single example, let us take his definition of the act of flexion and its importance in locomotion, for this is as incisive a description as any to be found among modern writers.

"Flexion is a change from a right line to an arc or an angle, straightening a change from either of these to a right line. Now in all such changes the flexion or the straightening

[1] For English readers the best translation of the *De Motu* and the *De Incessu* is that of A. S. L. Farquharson in vol. v of the Oxford edition of the Works of Aristotle (1912).

must be relative to one point. Moreover, without flexion there could not be walking or swimming or flying. For since limbed creatures stand and take their weight alternately on one or other of the opposite legs, if one be thrust forward the other must of necessity be bent. For the opposite limbs are naturally of equal length, and the one which is under the weight must be a kind of perpendicular at right angles to the ground. When then one leg is advanced it becomes the hypothenuse of a right-angled triangle. Its square then is equal to the square on the other side together with the square on the base. As the legs then are equal, the one at rest must bend either at the knee or, if there were any kneeless animal which walked, at some other articulation." (*De Incessu*, ch. 9).

Any comment upon the wisdom or clarity of this passage, which is typical of Aristotle's biological writings, would be superfluous.

The works of Hippocrates (460–370 B.C.),[2] of Aretaeus (fl. *c.* 200 A.D.),[3] and of Celsus (born *c.* 25 B.C.)[4] are disappointing from the viewpoint of muscle physiology. It is clear, however, that they were familiar with many of the more important disorders of locomotion, and they describe clearly certain forms of muscular rigidity and tetaniform convulsions, but none of these three authors appear to have held views on the *nature* of muscular contraction itself. Aretaeus, however, placed tetanus among the nervous affections because in these disorders the tendons and aponeuroses are periodically strained. He also clearly recognized the fact that paralyses of central origin are crossed, while those of spinal origin are not.

We may turn from these early observers to Claudius Galen (131–201 A.D.), "the father of experimental physiology." The physiological discoveries of Galen have been made the subject of several historical dissertations,[5] and are therefore well-known. We must pass over his description of the cranial nerves, of experimental hemiplegia, of the effect on respiration of section of the spinal cord at various levels, and of aphonia produced by section of the recurrent laryngeal nerve, to his experiments and observations

[2] Hippocrates with English translation by W. H. S. Jones (Loeb Classical Library) Heinemann; first 2 vols. published 1923. See also Francis Adams, *The Genuine Works of Hippocrates*, published for the Sydenham Society, 1849, 2 vols.

[3] Greek texts of Aretaeus were published in 1554 (Paris), in 1723 (Oxford) and in 1858 with an English translation by Francis Adams (London). A Latin text appeared in Venice in 1552.

[4] Ed. Princeps of Celsus (Latin), Florence, 1478; Aldine ed. 1528. The most scholarly translation is that of W. Frieboes (German), Braunschweig, 1906. English editions have appeared, such as that of James Greive, London, 1756. The best French translation is Daremberg's (Paris, 1859). The authority for the probable date of Celsus' birth is Allbutt (*Greek Med. in Rome*, 1921).

[5] Th. Meyer-Steineg, *Studien Zur Physiologie des Galens*. Arch. f. Geschichte d. Med., Leipzig, 1911–1913, Bd. 5, p. 172; Bd. 6, p. 417.

Allbutt, C. *Greek Medicine in Rome*, London, 1921.

Malloch, A. *Galen*. Ann. Hist. Med., N. Y., vol. 8, pp. 61–68, 1926.

on the contraction and tonic activity of muscle. Galen was probably the first to observe that after excision from the body a muscle may still contract when appropriately stimulated (mechanically). The passage in which this discovery is described may be quoted (*De Motu Musculorum*, Bk. 1, ch. viii).[6]

"If one sections transversely a dead muscle [*i.e.*, one freshly excised] which is thus not under voluntary control, one observes that it contracts toward its extremities, an event which appears, not without reason, to result from its innate properties. Therefore, if the body of a muscle has the power of contracting when isolated, what need then has it of the voluntary faculties for the production of movement, especially if the voluntary faculty derived from the soul is not functioning and the muscles yield mutually to each other in their movements. In fact, if one muscle or another *does* constantly that which it was designed *to do* [*i.e.*, contract], one cannot then distinguish such an affection from a *tetanus*. What is it, if not a tetanus, that causes the parts to be drawn involuntarily in the opposite directions by antagonistic muscles . . . . ? Accepting this hypothesis, there emerges a fact which is contradictory to the proceeding, for in this hypothesis the vigour of the voluntary faculty serves not only to move the muscles, but also to stop their movement. We find then, contradictions in many of the phenomena which we have observed. First, and the most grave, is that if the nerve which supplies the muscle is cut, at that instant the muscle becomes lengthened, and it remains forever in that state. Now if contraction is a property of the body of the muscle itself, and if extension results from a command of the will, extension ought to be abolished rather than contraction, since the nerve being cut, the communication between the principal and the nerve is interrupted; but the contrary is the case, for there is contraction in the muscle with an intact nerve, and extension of the antagonist."

Muscular rigidity and tetanic convulsions were well known to the ancients, as we have seen, and were carefully described by Galen as well as by Hippocrates. We have, therefore, in the above experiments of Galen, a clear attempt to apply the results obtained experimentally by stimulation of excised muscle to the clinical problem of spasticity and contracture, and the suggestion which Galen makes is singularly reminiscent of a modern controversy: "spastic contraction results from continuous stimulation." That Galen had in mind successive responses of muscle to successive stimuli as constituting a tetanus, is of course somewhat improbable.

When discussing the varieties of movement, Galen made four distinctions: (1) the movement of simple contraction; (2) lengthening, due to contraction of an antagonist, (3) passive movement, as when an arm drops under its own weight, (4) the "movement" by which, for example, an arm raised to the level of one's shoulder *is maintained in that position*. Galen

[6] A useful translation (French) of the chief works of Galen is that of Daremberg (2 vols., Paris, 1854–1856). He it was who once repeated Galen's physiological experiments in the Jardin des Plantes and is stated to have corroborated them all!

draws attention to the fact that this latter involves no gross movement, but rather the essence of movement, *i.e.*, static contraction, and to this he applied the word "tonus."[7] In so doing, Galen used the word in its strictly

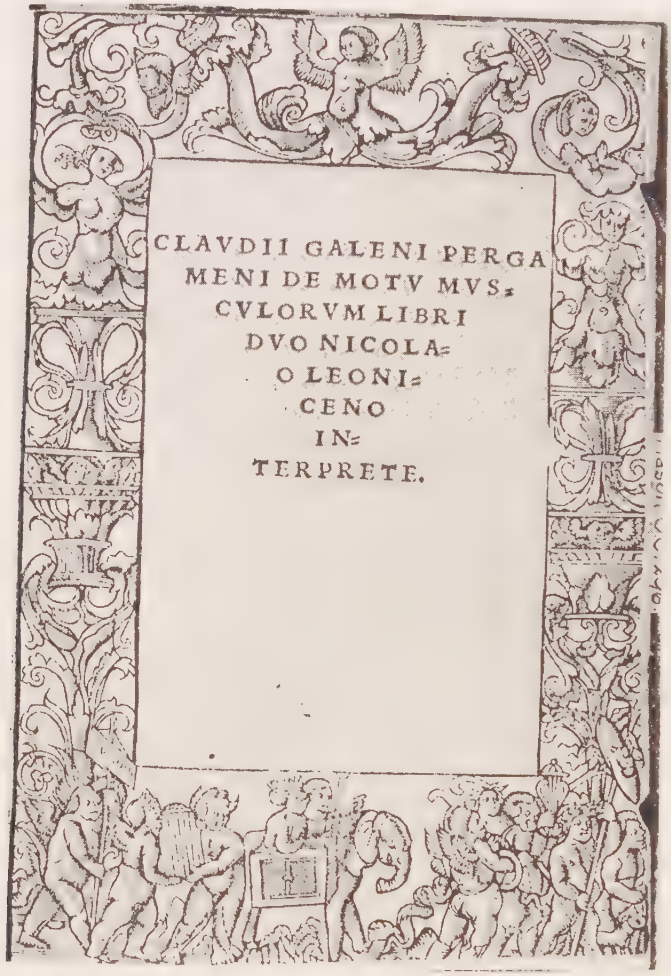
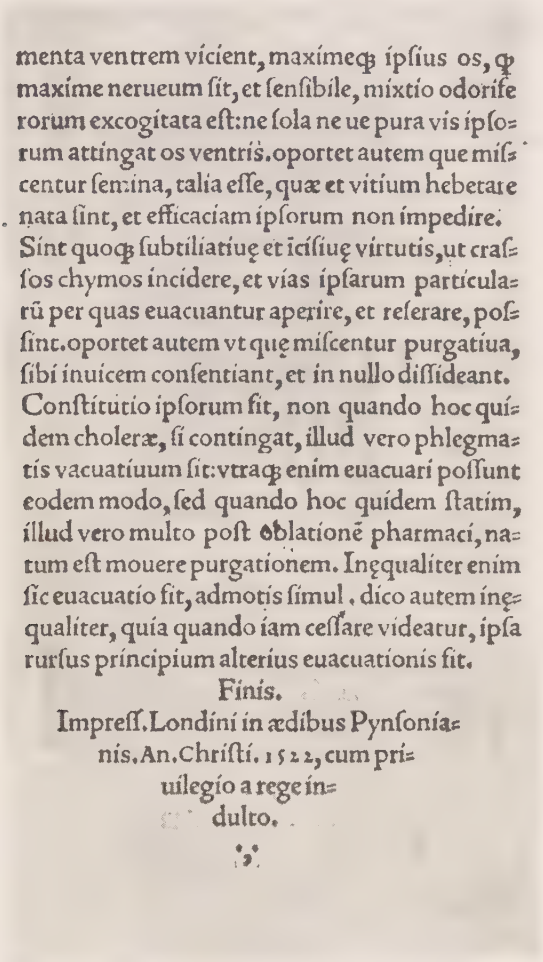


FIG. 1A. The title page of the first printed monograph on the physiology of muscle, being Galen's *De Motu Musculorum*. It was translated into Latin from the Greek original (MSS.), probably between 1509 and 1520, by Nicolaus Leonicenus, the medical humanist, and was published by his illustrious English pupil, Thomas Linacre, in London in 1522 at the press of Richard Pynson, one-time apprentice of William Caxton.

[7] See Sherrington's "Note on the history of the word tonus" in the *Contributions to Medical and Biological Research dedicated to Sir William Osler*, Bt., (i, p. 261), 1919.

modern sense, as implying "active posture," which in recent years has been investigated so thoroughly by Sherrington. Galen showed moreover that this tonus of a muscle disappeared forever when the motor nerve had been


menta ventrem vicient, maximeq; ipſius os, ꝙ
maxime nerueum ſit, et ſenſibile, mixtio odorife
rorum excogitata eſt: ne ſola ne ue pura vis ipſo=
rum attingat os ventris. oportet autem que miſ=
centur ſemina, talia eſſe, quæ et vitium hebetare
nata ſint, et efficaciam ipſorum non impedire.
Sint quoq; ſubtiliatiuę et iciſiuę virtutis, ut craſ=
ſos chymos incidere, et vias ipſarum particula=
rū per quas euacuantur aperire, et reſerare, poſ=
ſint. oportet autem vt quę miſcentur purgatiua,
ſibi inuicem conſentiant, et in nullo diſſideant.
Conſtitutio ipſorum ſit, non quando hoc quí=
dem choleræ, ſi contingat, illud vero phlegma=
tis vacuatiuum ſit: vtraq; enim euacuari poſſunt
eodem modo, ſed quando hoc quidem ſtatim,
illud vero multo poſt ꝺblationē pharmaci, na=
tum eſt mouere purgationem. Inęqualiter enim
ſic euacuatio fit, admotis ſimul. dico autem ineę=
qualiter, quia quando iam ceſſare videatur, ipſa
rurſus principium alterius euacuationis fit.

Finis.

Impreſſ. Londini in ædibus Pynſonia=
nis. An. Chriſti. 1522, cum pri=
uilegio a rege in=
dulto.

[Fig. 1B. The colophon of the '*De Motu*' giving the date of publication

cut. It is clear, also, from the quotation which has just been given, that Galen sensed the importance of reciprocal action of antagonistic muscles.

As the late Sir Clifford Allbutt pointed out, one finds time after time in Galen, on points of dispute, that "he appeals to his opponent to betake him-

self to experiment—to 'try,' and he tells him how and what to do and observe (*e.g.*, *Nat. Fac.* iii. 8). Guy of Chauliac was fully justified in his eulogy of Galen, 'fuit enim maximus in scientia demonstrativa.'"[8]

Available texts of these classical medical writers began gradually to find their way to medieval presses a few decades after the invention of printing. They could not be published, however, without laborious textual criticism, and for services in this field the world at large owes an incalculable debt to the labours of Nicolaus Leonicenus (1428-1524), the medical humanist of Ferrara. He diligently collected and compared the various manuscript texts of classical writers, devoting especial attention to the works of Galen. To Leonicenus we are indebted for the first translation into Latin of Galen's *De Motu Musculorum*. This was made probably between 1509 and 1520. For some reason, at present unknown, the work was not published in Italy. A possible explanation for this is the fact that Leonicenus had available only one manuscript of the work and this may have borne internal evidence of corruption.[9] In any case the translation was sent by Leonicenus to his devoted English pupil, Thomas Linacre, who published it in London in 1522. The title-page of the copy possessed by the Bodleian Library, Oxford, is reproduced in figure 1A.

Happy indeed was the fate which caused the first monograph on muscle physiology to be printed in England, where 150 years later Croone, Mayow and Glisson were to make such important contributions to the subject, and were to lay the foundation for a leadership in this field of physiology which is still maintained by English investigators. It is an interesting coincidence too that the founder of the Royal College of Physicians,—where annual lectures on "muscular motion" in memory of William Croone are still delivered,—should have been responsible for first publishing Galen's work.

The second edition of the *De Motu Musculorum* was published in Paris in 1528 at the press of Simon of Coline by Guenther von Andernach, the teacher of Vesalius. In this edition Linacre's preface, in which apology is made for the original manuscript text, was still retained. A later edition, edited by Jacobus Sylvius, who incorporated corrections from a (then) newly found Greek text, appeared at Lyons in 1549.[10] Perhaps as interesting as any of the early editions of this work is that of its first translation into a vernacular tongue (French), which was brought forth in 1541 at the celebrated press of Étienne Dolet by Jean Canappe, a physician of Lyons. The title-page of this work is reproduced in

[8] *Greek Medicine in Rome*, 1921, p. 292.

[9] Since that time other and better manuscript texts have made their appearance, and advantage of these was taken by Daremberg when making the French translation of 1856.

[10] Sylvius' corrected text was used by Conrad Gesner in his collected Latin edition of Galen's works which was published by Froben of Basle in 1562 (4 vols. folio).

figure 2. Christie, who devoted his life to the study of the biography and bibliography of Étienne Dolet[11] and his press, knew of but one copy (in 1899), and that incomplete, which

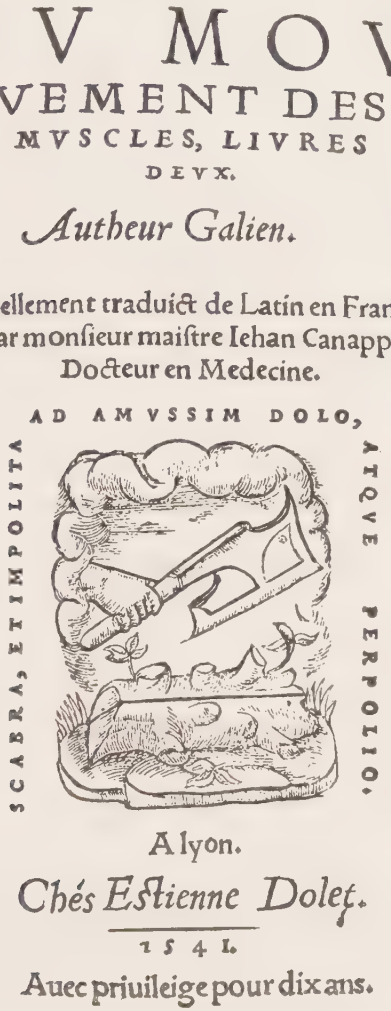


FIG. 2. The title page of Jean Canappe's French translation of Galen's work on muscles, published in 1541 at the press of Étienne Dolet (Lyons). This was the first appearance of the *De Motu Musculorum* in a vernacular tongue. As with the Latin edition of 1522, this French translation is also extremely scarce.

[11] *Étienne Dolet, The Martyr of the Renaissance, 1508–1546, A Biography*, by R. C. Christie, 2nd Ed. London: Macmillan, 1899.

was in the *Bibliotheque Nationale* (Paris). Since then a second copy has made its appearance, which is now in the possession of Doctor Edward C. Streeter of Boston, and I am indebted to his courtesy for permission to reproduce its title page (fig. 2). An undated edition of the Canappe translation was also published by A. Constantin of Lyons.[12] This probably appeared between 1543 and 1545. The present scarcity of all of the early editions of Galen on Muscular Movement bears ample testimony to the fact that they must have been eagerly read at the time of their appearance, but unfortunately we have little contemporary evidence as to the way in which they were received.

I have looked in vain through the works of the early Byzantine physicians, of whom Aëtius (*fl.* 500 A.D.), Alexander of Tralles (525–605), and Paul of Ægina (625–690) were the most important, for evidence of physiological experimentation. Though the knowledge of the nervous system displayed by Alexander was above that of the average low ebb of medicine in the seventh century, it was nevertheless derived almost wholly from Hippocrates and Galen, and there is little pretence to originality in either the work of Alexander or of Paul. The writings of the Arabian physicians are similarly disappointing.

For several centuries after the last of the Byzantine physicians, intellectual activity in the sphere of medicine and physiology ceased to exist, or whatever there was consisted, as is well known, in a mere transcription of Galen and Hippocrates and citation of them as authorities. The light of the Renaissance first descended upon Salerno in the tenth or eleventh centuries, but Salernitan physiology, if it existed, is lost. Not until we come to that unique figure of the sixteenth century, Andrea Vesalius (1514–1562), who at the age of 28 had dissected the whole of the human body and published his immortal work *De Humani Corporis Fabrica* (1543), do we find the spirit of experimental investigation once more reincarnated. The story of Vesalius which has been told so attractively by Roth,[13] Osler[14] and Foster (*334*), is too well known to be repeated.

It would be unjust to pass directly from the school of Salerno to Vesalius without mentioning the contributions of the early artists to our knowledge of muscular action. The first "medical" dissections of which we have accurate knowledge were those of Mundinus (1270) and William of Salicet (1275), but their interest centered almost entirely upon the interior of the body and (in the works of Mundinus) there is as a result scant mention of muscle structure. This is apparently true of all the dissections performed in recognized medical schools before the time of Vesalius, but with the advent of the Renaissance artists

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[12] Copies of this, and of the Sylvius edition, 1549, are in the Surgeon-General's Library at Washington.

[13] Roth, M. *Andreas Vesalius Bruxellensis*, Berlin: Reimer, 1892, viii + 500 pp., 29 Taf.

[14] Osler, W., *Evolution of Modern Medicine*, New Haven: Yale Univ. Press, 1921, xv + 243 pp.

there arose an intense desire to learn the mechanism of movement. The desire for detailed superficial anatomy had its origin with Giotto in 1300, and his successors, Massaccio and Masolino, added a further stimulus to this movement. The artist who first investigated by anatomical dissection the mechanical action of muscles was Piero Pollaiuolo (1443–*c.*1496), and his efforts were indeed richly rewarded by the faithful representation which his studies enabled him to make of power and movement. The precise myological detail which is found in his predecessor, Donatello (1386–1466), probably resulted, as it did with Myron,[15] from scrupulously accurate observation of superficial anatomy, for we have no evidence that Donatello actually dissected. Many other names of Renaissance artists who performed dissection of muscles with a view to studying their action might be mentioned, but this would be out of place in a brief historical account. We cannot, however, pass by Leonardo da Vinci (1452–1519) for in his notebooks are to be found accurate diagrams of the mechanical action of muscles which in many points compare favourably with the similar geometrical analyses made subsequently by Borelli.

It is generally conceded that a knowledge of structure must precede a study of function, and it is not therefore out of place to mention in an outline of muscle physiology the anatomists who first investigated the structure of muscles. After the artist dissectors, Vesalius stands supreme as a contributor to our knowledge of the structure of muscles; but we must not forget that Giambattista Canano (d. 1579), who was born in 1515, a few months after Vesalius' birth, also performed accurate dissections of human muscles, and the tragic story of the book,[16] in which he had intended to communicate his results to the world, makes it evident that Canano shares equally with Vesalius the credit of having been among the first to perform and to describe accurate anatomical dissections of the muscular system. Vesalius, however, claims our attention for another reason. In the last chapter of the *Fabrica* is described his physiological experiments on living animals. In this he confirmed many of the results of Galen but amplified them in many ways. Thus he found that by cutting or ligaturing one nerve or another, it is possible to abolish the action of the muscle which it innervates, and he observed that if the ligature was not tight the muscle recovered its action on loosening He observed also that the nerve sheath was not essential to its action, for the nerve continued to conduct after the sheath had been removed. Vesalius recognized that the fleshy parts of skeletal muscles were responsible for their contractile power and not, as Galen had supposed, the ligamentous elements which spread into the

[15] The question has often been raised as to whether the Greek sculptors performed dissections of muscles, and we have it on Cicero's evidence that Myron was taken with an intense curiosity to know the inside of man. Whether he ever satisfied this curiosity is not known.

[16] See Cushing and Streeter's facsimile reproduction of Canano's book (*Musculorum humani corporis picturata dissectio*), brought out in 1925 by Lier of Florence, Italy.

muscle from the tendon. It is clear from Vesalius' chapter on vivisection that he contemplated further investigation, and had fate but been kinder, Vesalius would undoubtedly have made other substantial contributions to nerve-muscle physiology.

"*Animal spirits.*"[17] Galen had taught that muscular contraction is brought about by "spirits," which passed from the brain to muscles through the nerves, causing the muscle as a whole to swell transversely and at the same time to shorten longitudinally. The belief that animal spirits cause contraction dominated physiological thought until the nineteenth century, and it proved the basis of discussion for all writers on the subject during the sixteenth and seventeenth centuries. The history of muscle physiology during these times centres largely around this one idea, and we may therefore proceed to trace its development.

The first of "modern" authors to publish a separate work on muscular activity was Fabricius of Aquapendente (1537–1619), the teacher of William Harvey. He attempted to analyze muscular mechanics along geometrical lines, but as this was done before the conceptions of Galileo had become established, we find in Fabricius little more than a repetition in slightly new form of what Galen had already taught. Outstanding developments in muscle physiology took place, however, in the middle of the seventeenth century. Steno in Denmark, Borelli in Italy, and Croone, Mayow, Willis, and Glisson in England, all contemporaries and all more or less stimulated by the mechanical conceptions of Galileo, set out to solve the problems of muscular contraction.

Of this remarkable constellation of muscle physiologists the first to communicate his results to the world was the illustrious William Croone (1633–1684), founder of the Croonian Lectures. In a book, *De ratione motus musculorum*, published (anonymously) in London in 1664 (the title page of which is shown in figure 3), we find the views of this singular man set forth. Though perhaps Croone had not the originality of Steno or the capacity of Borelli, for meticulous mathematical detail Croone's little work marks the opening of a new era in the history of muscle physiology. He grasped the importance of the contractility of the fleshy portions of the muscle, and gave credence, though apparently with some mis-

[17] In discussing the work of Steno, Willis, Glisson, and Borelli, I have drawn upon Daremberg's (*220*) Soury's (*960*) and Foster's (*334*) histories. In every case, however, I have attempted to verify all statements and translations by appeal to the original works. In the selected passages from Steno and Borelli, I have taken advantage of Foster's excellent translations. Bibliographical descriptions of the works mentioned will be found at the end of the introduction (p. 53).

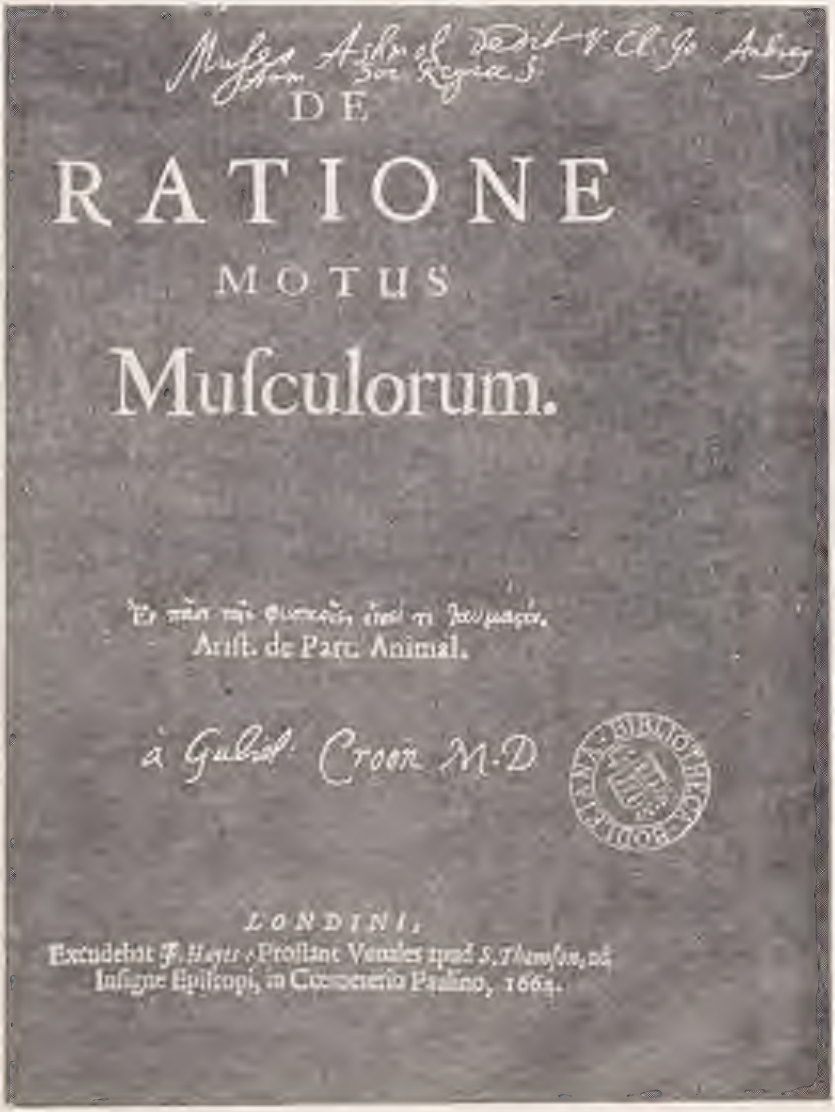


FIG. 3. The title page of William Croone's *De ratione motus musculorum*, published anonymously in London in 1664.

givings, to the Galenical postulate of animal spirits as the causation of contraction. He appreciated the necessity of the circulation for the proper functioning of a muscle and constructed a most admirable diagram in

which he represented his beliefs concerning the interaction of the substances derived from the blood with animal spirits conveyed by the nerves. He

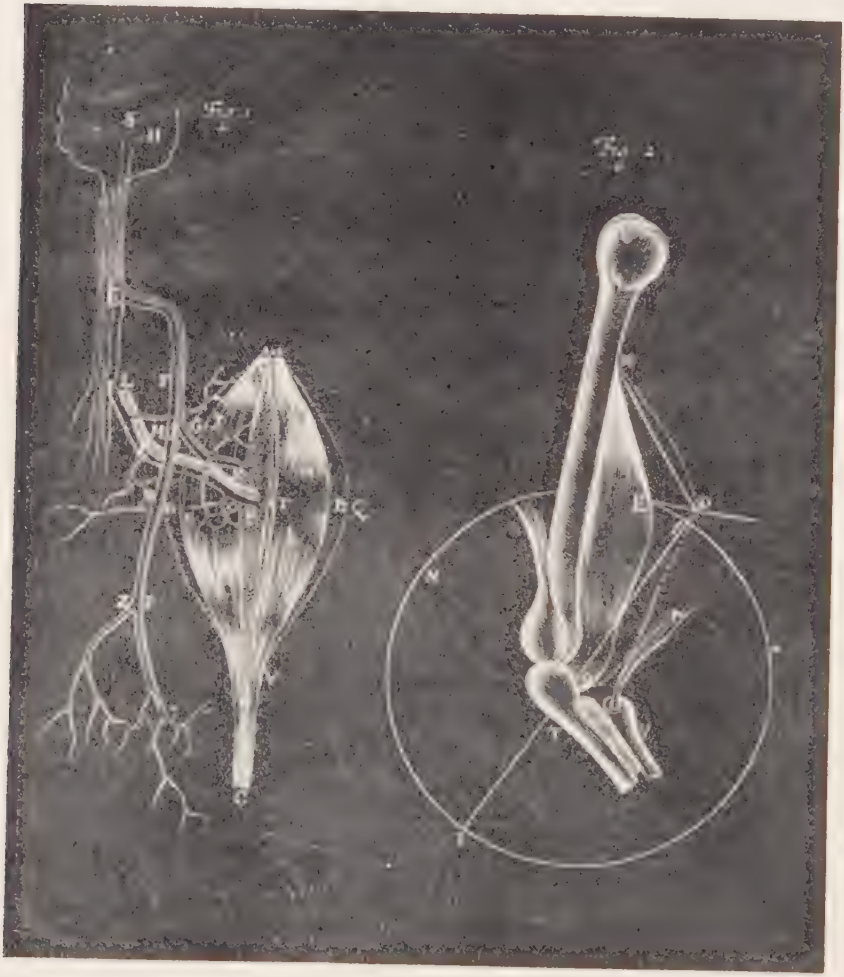


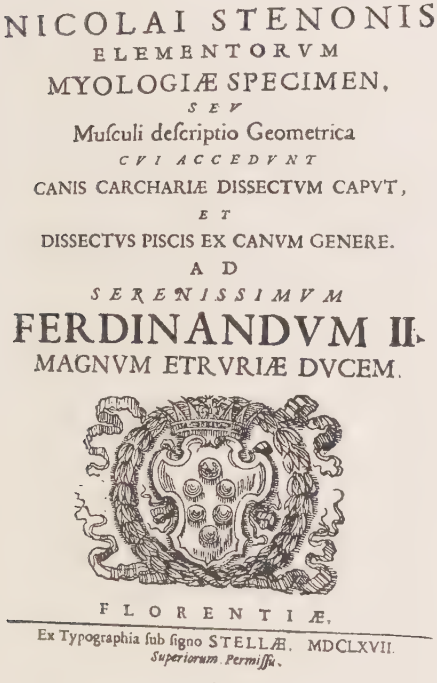
FIG. 4. The engraved plate from Croone's book illustrating (*fig. 1*) the blood-vessels and nerve supply of a muscle, and (*fig. 2*) the direction of forces exerted by certain muscles of the elbow joint.

also attempted geometrical analyses of muscular action (see fig. 4) along the lines subsequently followed in greater detail by Steno and Borelli.

Croone was on friendly terms with Steno, and one of Steno's letters to

Croone, written from Rome, May 23, 1666, is preserved in the *Philosophical Transactions of the Royal Society* (vol. 1, p. 377).

A professor at Gresham College during the greater part of his life,[18] Croone maintained to the end an active interest in the physiology of muscle, and when he died in 1684 he left in his will a plan for annual lectureships on the physiology of "muscular motion" to be delivered each year at the Royal


NICOLAI STENONIS
ELEMENTORVM
MYOLOGIÆ SPECIMEN,
SEV
Musculi descriptio Geometrica
CVI ACCEDVNT
CANIS CARCHARIÆ DISSECTVM CAPVT,
ET
DISSECTVS PISCIS EX CANVM GENERE.
A D
SERENISSIMVM
FERDINANDVM II.
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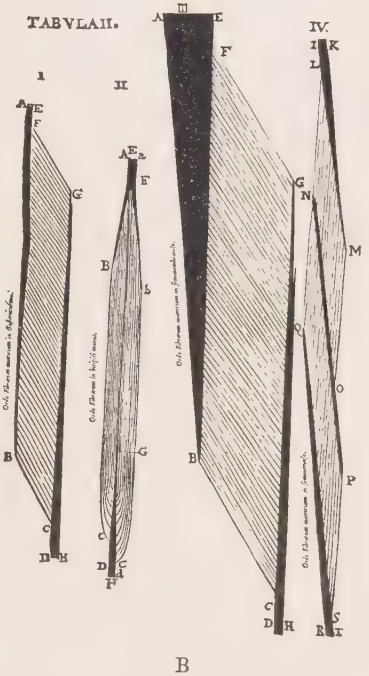
Ex Typographia sub signo STELLÆ. MDCLXVII.
Superiorum Permissu.

A



B

FIG. 5. A. The title page of Nicolas Steno's *Elementorum Myologiae Specimen*, published in Florence in 1667.

B. Steno's diagram of the arrangement of the fibres in various muscles. Taken from the second edition, Amsterdam, 1669; in the first (1667) the same diagram is given but the muscles are not labelled as in the 1669 edition.

Society and at the Royal College of Physicians. Financial provision for these lectureships was made some twenty years after Croone's death by his widow, who had married Sir Edwin Sadlier, *Bt.* It is literally true that the history of muscle physiology in the eighteenth, nineteenth and twentieth

[18] For the life of Croone, see John Ward's *Lives of the Professors of Gresham College*, London, 1740, p. 321.

centuries has been largely developed at these annual occasions. No other field of physiology has had a more ancient or unique lectureship devoted to its advancement, and the many contributions to this sphere of knowledge made by Englishmen would appear to be due in no small measure to the stimulating influence of Croone's bequest.

Nicolas Steno (1638–1686), or Stenson, as he is known to some, had become interested in the problem of muscular movement at the same time as had Croone, and published a preliminary description of his work[19] in the same year (1664) that Croone's book was issued. Steno's important contribution, the *Elementorum myologiae specimen*, did not appear, however, until 1667. In this he laid the foundation of muscular mechanics as we now know it, and introduced many new and important conceptions which reflect great credit upon his ingenuity. Equipped with a microscope, he at once grasped the significance of the fibrillar structure of skeletal muscle and realized that the tensile forces developed in each individual *fibra motrix* (as he called the structural units) became summated into the response of the muscle as a whole. In muscles in which the fibres are pennate in arrangement he realized that the maximum resultant tension could only be developed provided the muscle shortened but little. Muscles of this sort were therefore primarily tension muscles (*i.e.*, designed for "isometric" contraction), while parallel-fibred muscles are designed for more extensive shortening. One of Steno's diagrams is reproduced in figure 5B. As Foster has pointed out, Steno's *fibra motrix* was in reality a motor fasciculus in modern terminology, and his "most minute fibrils" were our elementary muscle fibres. This, however, does not rob Steno's observations of their importance, for the recognition that the tension developed by a muscle is the resultant of the individual forces of its fibre constituents is a fundamental contribution to muscle physiology. Since he was enamored with mechanical philosophy of Galileo, we find his book largely taken up with elaborate mechanical and mathematical expositions, but his interest was centred throughout upon the individual *fibra motrix*. He observed that when a long muscle is cut up lengthwise by scissors into three or four pieces each separate part may be made to contract. He thus demonstrated that contractility must reside within the muscle substance and is not therefore dependent upon the integrity of the entire muscle machine. Moreover, Steno had grave doubts as to the Galenical hypothesis of animal spirits, as we shall see in the following remarkable passage from his work (*Element. Myol. Spec.*, 2nd ed., p. 83 *et seq.*).

[19] Steno. *De musculis et glandulis observationum specimen cum epistolis duabus anatomicis.* Amsterdam: Pierre le Grand, 1664. 12°.

"Concerning the fluid of muscles how uncertain, or rather how wholly wanting, is our knowledge. Fluid certainly exists in the fibrillae of which the motor fibres are composed and between the fibrillae, also between the motor fibres themselves, in the membranous fibrillae [that is the connective tissue], and between the membranous fibrillae; but in truth it is by no means clear whether these fluids are all of one kind or whether just as they are distinct in the seats which they occupy so they differ in material properties. Nor is it known whether any of these fluids are really like any one of the fluids so far known to us. Animal spirits, the more subtle part of the blood, the vapour of blood, and the juice of the nerves, these are names used by many, *but they are mere words, meaning nothing.* Some going further bring forward saline and sulphureous particles or something analogous to spirits of wine. Such things may perhaps be true, but are neither certain nor adequately distinct. Experience teaches us that a dose of spirits of wine restores exhausted powers, but who shall have determined whether that which restores the fluid spirit is to be ascribed to this said humour which we call spirit or to some other material or is joined to it through some other cause? As the substance of this fluid is unknown to us, so is its movement undetermined, since neither by sure reasoning nor by experiment has it been ascertained whence it comes, whither it tends, where on its departure it betakes itself. . . . . There remains another difficulty of no less moment not yet cleared up, namely in what respect the movement of the fluid in a muscle while it is contracting differs from the movement of the fluid in the same muscle when it remains quiet, uncontracted. Is its quantity changed? or does it remain the same? Is the fluid after the event, supposing it remains, the same as before the event? Does the fluid move because the muscle contracts, or does the contraction of the solid proceed from the movement of the fluid?" (Foster's translation.)

Quite a different figure from Steno was Croone's fellow countryman, Thomas Willis (1621–1675), who published a work on muscular movement in 1670. A devout Galenist and a successful practitioner, he had little of the originality or scientific insight possessed by his contemporaries. He was nevertheless an excellent anatomist, and to him we are indebted for the first complete description and enumeration of the cranial nerves. He reiterated, nevertheless, with several interesting but rather speculative modifications, the Galenical notion of animal spirits, as is evident from the following quotation (*1050*).

"The animal spirits carried from the brain by the channels of the nerves to a muscle, caught up by the membranaceous fibrillae, and carried by means of these to the fibres of the tendon, are then plenteously stored up as it were in suitable storehouses. These spirits, being by nature exceedingly active and elastic, upon expanding as their power and opportunity permit, leap into the fleshy fibres, and presently afterwards, their impetus being exhausted, falling back, they retreat again into the tendons; and this is repeated again and again. When however the animal spirits at the bidding of the instinct to bring about movement rush from the tendinous to the fleshy fibres, they there meet with active particles of a different nature supplied by the blood, and forthwith the two mixing, effervesce, so that out of the struggle and agitation of the two, the fleshy fibres, previously lax and porous, are stuffed full and thrown into corrugations, and all the fibres being thus corrugated at the same time, the contraction of the whole muscle is brought about. The contraction

being finished, the pure spirits which remain for the most part retreat again into the tendinous fibres, the remaining particles being left among the fleshy fibres. The loss which has occurred among the latter is made good by the blood, that among the former by the nerves." (Foster.)

TRACTATUS QUARTUS.

De MOTU MUSCULARI

Et SPIRITIBUS ANIMALIBUS.

Obiter DE MOTU CEREBRI:

Nec Non De Usu. LIENIS & PANCREATIS.

PARS SECUNDA.

Fig. 6. The title page of John Mayow's tract on muscular movement, it being the fourth of his *Tractatus Quinque* which was published at Oxford in 1674.

In John Mayow (1645–1679) we find an original mind endowed with all the essentials of genius. His observations on the nitro-aërial spirit (oxygen)

and his theories of respiration, lost as they were to the scientific world for a hundred years, are now at last well-known, but his contributions to muscle physiology are less well-recognized. The title page of his tract on muscle is given in figure 6. He read eagerly the works of his contemporaries and apparently saw at once both the strength and the weakness of their arguments. Thus, in commenting upon the views expressed by Willis in the above quotation, he remarked,

"The theory of the learned author is certainly very ingenious, but I am not sure that it is in the same degree in accordance with truth. For, in the first place, the inflation of the fibres in the way described is beset with various difficulties, and these of no small weight. For if a muscle is contracted by the inflation of its fibres, it would necessarily follow that, being distended towards the outside in its contraction, it would swell into a much greater size; but it has been found by observation that a contracted muscle is drawn more closely together and becomes hard, and that, if it does not become smaller, yet certainly does not swell up to such an extent as would be required for its contraction, if that were brought about by the inflation of its fibres, as has already been noted some time ago by Lower. But that in some contracted muscles we seem to feel a tumour, does not, I think, come so much from their swelling as from the movement of the belly of the muscle, in its contraction, towards the fixed tendon, so that the ascent of the belly of the muscle caused in this way, raises a hand placed on the muscle and simulates a tumour. Further, if some elastic matter contained within the passages of the fibres inflated them in the way described, how could it be that the fibres should in a moment subside again, as happens in the glance of the eye and in other instantaneous contractions of the fibres? For neither can I comprehend how that elastic matter should in an instant inflate the fibres and again extricate itself from their passages, for if an easy way out of the fibres lay open to that rarefied matter, it would pass quickly through the fibres and not properly inflate them. . . . . Finally, as to the part of the muscle which primarily undergoes contraction, it is probable that not so much the fibres, as the fibrils inserted transversely into them, chiefly undergo contraction, as will be shown afterwards."

Though Mayow's beliefs as to the participation of his nitro-aërial spirit in the contractile process may be looked upon as somewhat speculative, Mayow nevertheless perceived, and not too vaguely, the fact that muscular energy depends upon a supply of material brought to it by the blood system. This is illustrated in many passages in his work. He realized that the functional activity of a muscle becomes greatly impaired on stopping the circulation,—an observation long overlooked. It is evident from the passage which we have quoted that he was probably familiar with the belief that a muscle does not increase in volume during contraction and is therefore probably not dependent upon the flow of animal spirits from the brain. Whether or not he demonstrated this himself is unknown; the proof of it is generally accredited to Mayow's contemporary, Francis Glisson, whom we must now consider.

Important contributions to the physiology of muscular contraction were also made by Francis Glisson (1597–1677). A man of exceptionally wide philosophical outlook, it is interesting to note that he realized clearly that knowledge of muscle physiology was then in its inception; "the proof," he said, "has only just begun, and it cannot be supplied in full by an old man like myself or by the hand of any single man." He then expressed the significant hope, "that the Royal Society and other inquirers after truth will be moved to furnish it." Through careful experimentation and logical reasoning Glisson was led to an unusual conception of the properties of muscular tissue which anticipated modern teaching by nearly a hundred years.[20] He argued that a given tissue is never provoked into activity unless it is irritated, and in order to have the power of being provoked into activity a tissue must have a special property which he designates irritability. Thus the conception of irritability may be traced not to Haller, as is sometimes stated, but to Glisson. Glisson's most important contribution, however, was of another sort. Willis, as we have seen, had reiterated the Galenical view that contraction is the result of flowing of spirits into the muscle through the channels of the nerves. If this were the case, Glisson contended, the muscle should increase in volume when in activity. On subjecting this possibility to experimental test he found that the volume of a muscle if anything diminishes somewhat, when it contracts. The experiment is so important that it is best described in his own words.

"But indeed this explosion and inflation of spirits has now for some time past been silenced, convicted by the following experiment. Take an oblong glass tube of suitable capacity and shape. Fit into the top of its side near its mouth another small tube like a funnel. Let a strong muscular man insert into the mouth of the larger tube the whole of his bared arm, and secure the mouth of the tube all round to the humerus with bandages so that no water can escape from the tube. Then pour water through the funnel until the whole of the larger tube is completely filled, and some water rises up into the funnel. This being done, now tell the man alternately to contract powerfully and to relax the muscles of his arm. It will be seen that when the muscles are contracted the water in the tube of the funnel sinks, rising again when relaxation takes place. From which it is clear the muscles are not inflated or swollen at the time that they are contracting, but on the contrary are lessened, shrunk, and subsided. For if they were inflated the water in the tubule so far from sinking would rise. From this therefore we may infer that the fibres are shortened by an intrinsic vital movement and have no need of any abundant afflux of spirits, either animal or vital, by which they are inflated, and being so shortened carry out the movements ordered by the brain."

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[20] Sherrington. *Note on the history of the word tonus. Contributions to Medical and Biological Research dedicated to Sir William Osler,* Bt., (vol. i, p. 261), 1919.

The importance of this experiment will be considered later when dealing with the observations of Borelli and Swammerdam.

We must now pass to Giovanni Alphonso Borelli (1608–1679). The story of his interesting life has been told by Foster and others and need not detain us here. It is important to recall, however, that while his investigations upon muscle physiology were commenced early in life and were apparently ready for the press as early as 1662, as noted by Bellini (then a student of Borelli),[21] various circumstances combined to prevent their publication

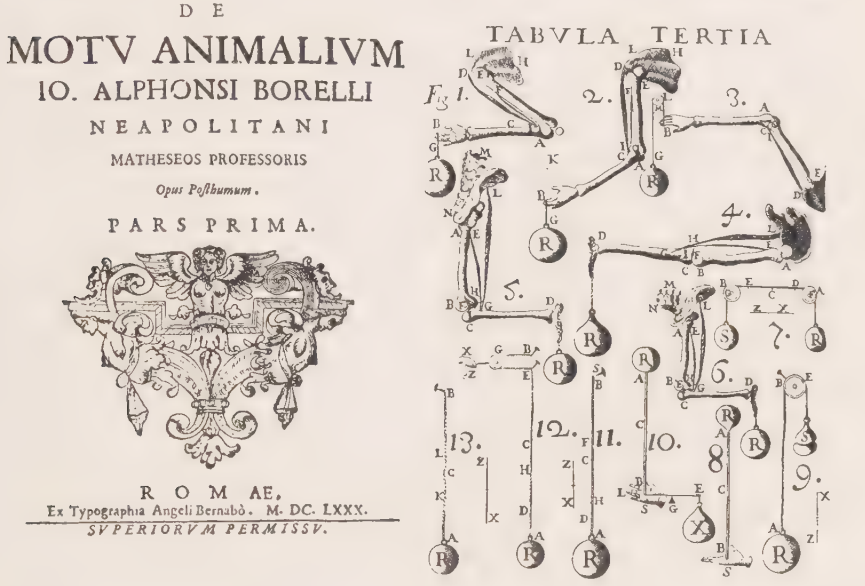

FIG. 7. The title page of Borelli's book with one of his plates illustrating several of the mechanical "propositions" relating to muscular action considered in the text of his *De Motu Animalium* (1680).

until a year after his death. The first edition of the *De Motu Animalium* appeared in Rome in 1680. This is probably the reason why he failed to discuss the investigations of his contemporaries more extensively than he did. It is true that he acknowledged the work of Steno and adopted his conception as to the structure of muscle (Lib. I, Prop. I–V), but I have been unable to find in his work any reference to Croone, Mayow, Willis, or Glisson. The failure to mention Glisson's demonstration of the constancy of muscle volume during activity is of course understandable in view of the

[21] Laurent, Bellini. *Exercitatio anatomica de structurâ et usu renum.* Florence, 1662.

fact that it appeared somewhat obscurely in a treatise on the stomach and intestines only two years before Borelli's death. Glisson's discovery, as we shall see, would have overthrown many of Borelli's beliefs concerning muscle, especially his hypothesis as to the causation of contraction. It is accordingly important, in considering the work of Borelli, to realize that he was separated from the other muscle investigators, and that his book was largely written before their work had appeared. The numerous tragedies which befell Borelli in his declining years undoubtedly embittered him and made him lose interest in his scientific contemporaries. We cannot but lament that in old age he did not have more ample opportunity, so essential for scientific work, of exchanging ideas with his fellow workers.

The *De Motu Animalium*, a large book in two volumes, is chiefly devoted to the elucidation of two main subjects, namely, the purely mechanical problem of tensile forces presented by various muscles, and secondly the more obscure question of the causation of contraction. The first volume is largely concerned with somewhat special geometrical analyses. He took exception to certain of Steno's mathematical deductions, but on these controversial points his reasoning is often obscure. He recognized the fibrillar structure of muscle and appreciated, as had Steno, the importance of focussing one's attention upon individual muscular constituents in order to gain an adequate comprehension of the behaviour of the muscle as a whole. He emphasized that the fleshy portions of the muscle were responsible for the development of tension rather than the fibrous aponeuroses (Lib. I, Prop. II). In figure 7 one of Borelli's diagrams representing various problems of muscular contraction is reproduced.

In his theory of the contractile process, however, Borelli was little in advance of Galen. He argued that it would be impossible to think of contraction as due merely to a displacement of the internal fluids and structures of the fibre, but that some "essence" or fluid must cause an inflation of the muscle fibres in order to cause shortening (see esp. Lib. II, Prop. XV). Adopting this as his working hypothesis, he developed at great length the mechanical consequences of his belief. His views are best illustrated by selecting a passage from his work.

"Since all muscles, with some few exceptions, do not manifest vital movement otherwise than in obedience to the will, since the commands of the will are not transmitted from the brain which is the instrument of the sensitive, and the seat of the motive soul, by any other channels than the nerves as all confess and as the most decided experiments show, and since the action of any incorporeal agency or of spirituous gases must be rejected, it is clear that some corporeal substance must be transmitted along the nerves to the muscles or else some commotion must be communicated along some substance in the nerves in such a way that a very powerful inflation can be brought about in the twinkling

of an eye. And since the inflation, hardening, and contraction do not take place in the channels which serve for bringing them about and in which the motor influence resides, namely, in the nerves themselves, but takes place outside the nerves, namely, in the muscles, it is evident that the substance or the influence which the nerves transmit is not taken by itself alone sufficient to bring about that inflation. It is necessary, therefore, that something else must be added, something which is to be found in the muscles themselves; or that in the muscles there is some adequate disposition of material so that on the arrival of the influence transmitted by the nerves there takes place something like a fermentation or ebullition, by which the sudden inflation of the muscle is brought about. That such an action is possible is rendered clear by innumerable experiments which are continually being made in chemical elaborations as when spirits of vitriol are poured on oil of tartar; indeed all acid spirits when mixed with fixed salts at once boil up with a sudden fermentation. In like manner, therefore, we may suppose that there takes place in a muscle a somewhat similar mixing from which a sudden fermentation and ebullition results, with the mass of which the porosities of the muscle are filled up and enlarged, thus bringing about the turgescence and the inflation. . . . . In the same way, if one of the extremities of the nerve fibre be compressed or pushed, or struck or pinched, forthwith the commotion and concussion or undulation ought to be communicated right to the other end, because by reason of their contiguity, the parts lying first in an ordered series by pressing on those following, communicate the blow and the impulse right to the end. . . . . And on the other hand when the extremities of the sensory nerves which end in the skin, nose, ears or eyes, are compressed or struck or titillated, it necessarily follows that forthwith the concussion, undulation, or titillation of the spirituous juice contained within the tubules is conveyed along the whole length of the nerve and reaches the particular part of the brain to which the nerve fibres are joined. And here the faculty of the sensitive soul according to the region of the brain thus percussed, according to the vehemence of the blow and the fashion and mode of the motion, is able to form a judgment concerning the object causing the movement." He insists that the "juices, however spirituous and active, are always corporeal and cannnot act at a distance, and cannot, without physical contact, increase, intensify, or depress the animal spirits; it is by means of their corporeal presence that they either increase the animal spirits which are also corporeal, mixing themselves with them, or expel them, or transform them. Wherefore it cannot be conceived that nervous action can take place without some local movement of the nervous juice passing along the whole length of the nerve right to the brain."

Borelli's conclusions illustrate how far one can go astray through admitting an unsound initial premise, and how a man's whole subsequent experimental career may be coloured by an inadequate working hypothesis, adopted early. It would be grossly incorrect, however, to imply that Borelli's work was without value. He added much to muscular mechanics and dealt with many special problems which Steno had not touched. Moreover, in his separate propositions one frequently encounters observations of the greatest shrewdness (*e.g.*, Lib. I, Prop. VII). He recognized the tonus of muscles and suggested that tonic contraction served to prevent the overaction of antagonists (see Lib. I, Prop. CXXXI, *et seq.*). Sherring-

ton[22] has pointed out that Borelli grasped the modern conception of "tonus" (*actio tonica*) as implying "postural" contraction and cites the following quotations from the '*De Motu*' as proof (Lib. I, Prop. CXXXVI): "Therefore the falling forward is prevented solely by the extensor muscles, and not in fact by the tonic action of extensors and flexors operating concurrently. . . . . Therefore men do not maintain station by the tonic action of all antagonistic muscles, but by the operation of all the extensor muscles and some of the flexors, while some of the flexors remain inoperatively at rest." This was a distinct advance upon Galen's analysis of animal posture.

In this connection it is interesting to realize that Sir Thomas Browne (in 1646) appreciated the significance of Galen's observation on "active posture." Thus in the *Pseudodoxia Epidemica* (Bk. III, Ch. I), Browne says: "For station is properly no rest, but one kinde of motion, relating unto that which Physitians (from Galen) doe name extensive or tonicall; that is, an extension of the muscles and organs of motion maintaining the body at length or in its proper figure; wherein although it seem to be unmoved, it is neverthelesse not without all motion; for in this position the muscles are sensibly extended, and labour to support the body; which permitted unto its proper gravity, would suddenly subside and fall unto the earth, as it happeneth in sleep, diseases and death. From which occult action and invisible motion of the muscles in station (as Galen declareth) proceed more offensive lassitudes then from ambulation."

We cannot leave the seventeenth century without mentioning the name of one who appealed time after time to direct experiment to answer the many questions presented by contracting muscles. This was Jan Swammerdam, the gifted naturalist of Holland. His experimental ingenuity and penetrating insight clearly surpassed that of any of his contemporaries, not excepting Steno and Glisson. Born in 1637 in Amsterdam, we find him in Paris in 1664 living, in the house of the celebrated Melchisedech Thévenot, with his Danish neighbour and friend, Steno. This was the year in which the latter had published his first contribution to the physiology of muscle (see above). It is evident from Steno's references to Swammerdam (*Element. Myol. Spec.*, 1669, Amsterdam, pp. 78, 79) that they had long been friends and that Steno had witnessed some of Swammerdam's early experiments. Swammerdam himself states that he commenced experimenting with the muscles of frogs in 1658 (at the age of 21). However, his book, the *Biblia Naturae*, in which the experiments on muscle were described, was not published until 1738, 58 years after his death (1680), when it was brought out by his countryman, Hermann Boerhaave. Some of the observations therein recorded, such as

[22] *Contributions to Medical and Biological Research dedicated to Sir William Osler*, Bt., vol. i, p. 263.

the discovery of the red blood cells (1658), are dated, but there is little, apart from the date of their commencement, to give us a clue as to the time in which his important observations on muscle were made. It is likely however, that the experiments were performed before 1664; so Swammer-

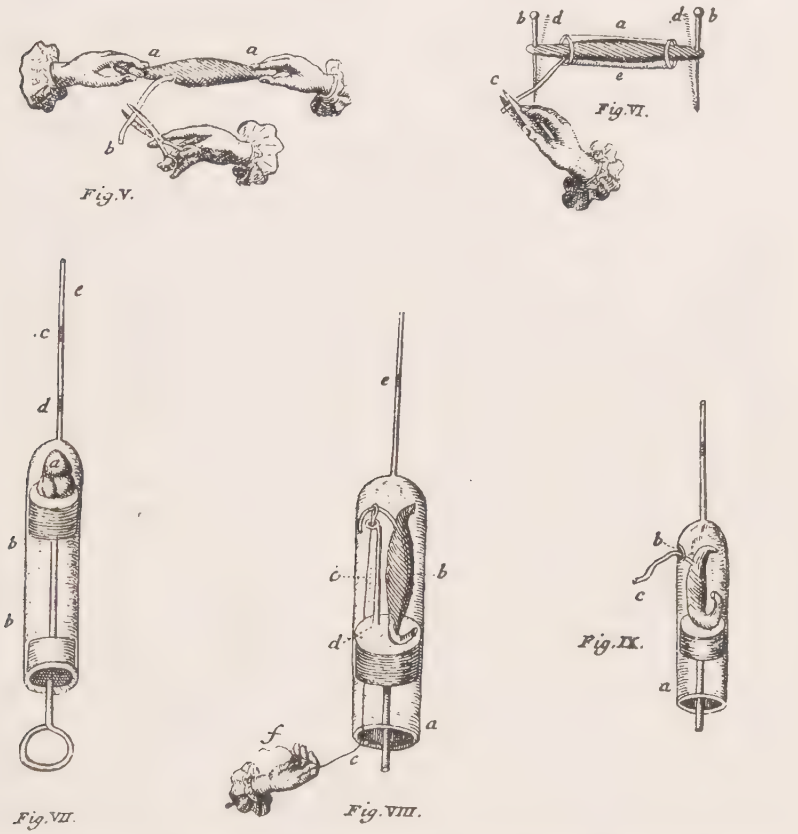

FIG. 8. Swammerdam's figures representing, among other things, his method of demonstrating the absence of volume changes during activity of muscle. See quotation from his work.

dam deserves to be grouped in time with Croone, Steno, Mayow, Borelli, and Glisson.

The above figures from Swammerdam's *Biblia Naturae* illustrate his method of investigating the problem of muscle volume. The experiments

are so well conceived and so clearly described, that we cannot do better than quote his own description.[23]

"If one selects a skeletal muscle in the place of a heart, one can proceed as indicated in figure VIII. The glass container, *a*, holds within it the muscle, *b*. The nerve, which hangs inside, is supported without injury or pressure by a fine silver wire, *cc*, which I draw through the eye of the brass rod that is soldered to the piston-head of the syringe, *d*. When everything is thus ready and arranged, a droplet of water, *e*, can be admitted through a small clean funnel into the fine tubule. If the long silver wire, which passes through the eye of the brass rod downwards between the piston-head and the inner surface of the syringe, is now drawn by the hand, *f*, until the nerve becomes stimulated [pressure], one then observes that the muscle contracts just as in the case of the inflated heart, and that the droplet of water does not rise, but actually sinks somewhat. However, this experiment is very ticklish and so many adverse conditions arise and one must proceed so carefully, that the operator readily becomes vexed with it. Therefore, I have devised another easier method. A similar glass syringe, shown in figure IX-*a*, is selected and a small hole is made at its far end by means of a diamond. Through this opening a stretch of nerve, *c*, is passed. If the nerve is stimulated, the muscle moves; air, however, can easily enter, which would prevent movement of the drop, so one must stop up the hole around the nerve. This is easily accomplished with isinglass and paste. Then, if I am truthful with you, *I must confess that the drop of water sinks so little that one can scarcely observe it.*"

It is thus evident that Swammerdam demonstrated the constancy of muscle volume during activity, at least fifteen or twenty years before Glisson's proof of it was published. Swammerdam's use of an excised muscle was, in addition, more convincing than Glisson's demonstration with the intact human arm; moreover, the method employed by Swammerdam is that still used in physiological classrooms. Swammerdam, as his figure indicates, also used the same device for watching the heart-beat. Had he but perfected a recording device, the technique of the manometer and of plethismographical recording might have been developed nearly two centuries before it was.

The beginning of the eighteenth century witnessed the publication of George Baglivi's (1668–1707) two important tracts, the *De Fibra Motrice et Morbosa* and the *De Anatome Fibrarum, de Motu Musculorum*, etc., both appearing first in 1700 and reappearing with additions in 1701. In the former, Baglivi distinguished between what we now term "striated muscle" and "smooth muscle," describing the gross and minute (microscopical)

[23] This passage is to be found on pages 849–850 of the original 1738 edition of the *Biblia Naturae*. It is also included in a Dutch-German selection from the *Biblia Naturae* reprinted in vol. i, of *Opuscula Selecta Neerlandicorum de Arte Medicorum*, Amsterdam: Rossen, 1907. I have not yet seen the English translation of the *Biblia Naturae*, which appeared in London in 1758.

appearance of the constituent fibres. He insisted that the former were designed for the execution of quick movements while the latter, being "membranous," subserved functions requiring long-maintained activity. We do not, however, find him speculating on the question of tonus. He observed also (and quite independently of Swammerdam) that without the "assistance" of a nerve, isolated pieces of heart muscle "tremble and oscillate" (fibrillation?) and often maintain with great regularity alternate movements of contraction and relaxation. Baglivi also noted that excised bits of skeletal muscle contract on being touched "without the soul's having any share in it, or even being sensible of it." His physiological discoveries (which were numerous in other fields as well) have never received adequate recognition; his name, as with Croone and Whytt, not being mentioned in Foster's *History of Physiology* (*334*).

It was Leeuwenhoek, however, who gave the first adequate description of the microscopical appearance of skeletal muscle fibres. Though he had published several previous observations on the subject, his most important contribution appeared in 1715 in the *Philosophical Transactions of the Royal Society* (*627*). He recognized longitudinal striations, but believed that the transverse "striations" represented the successive turns of a spiral thread twisted around the fibre. We shall see that this early view as to the structure of the fibre had been lately revived by Tiegs (*980*). Leeuwenhoek also demonstrated the existence of the sarcolemma.

One might dwell far longer on Swammerdam's, Baglivi's and Leeuwenhoek's physiological investigations, but space forbids. After their death, though the interest in the problem of muscular movement did not diminish, there are few contributions of moment until we come to von Haller and Robert Whytt. In the early years of the eighteenth century the problems of muscular movement were, however, actively discussed, often acrimoniously, by many writers, especially in England. A controversy, for instance, arose between Bryan Robinson[24] and an unknown writer of Dublin over the existence of animal spirits. Also an interesting discussion of muscular contraction was written in 1708 by James Keill (*544*). This author made calculations of the numbers of fibres in certain muscles and from these deduced the amount of tension developed by each individual fibre in lifting a given weight. He conceived of each fibre as a potential bladder which normally was stretched out so that its two walls approximated each other in a line. On contraction each fibre became inflated, tending to become spherical (thus shortening). The mathematical consequence of this hypothesis was that a muscle could not shorten to more than two-thirds its greatest length,

[24] Robinson, B. *A treatise on the animal oeconomy.* Dublin, 1732.

i.e., by about one-third. He tested this erroneous hypothesis experimentally and believed that he had proved it. Also one finds in this work an excellent description of what is referred to in this monograph as "multifibre summation." Other contributions were made by Bernouilli,[25] William Cowper,[26] and by Richard Mead, but they are of little consequence except as they illustrate the influence of Croone, Steno and Borelli.

By some curious mischance not adequately explained in Weld's *History of the Royal Society*, or in Ward's life of Croone (*loc. cit.*), the first of the Croonian Lectures was not given until 1738. It was delivered by one Alexander Stuart of Edinburgh, his title being "On the motion of the heart founded on animal observations and experiments." Fortunately, it was published in the *Philosophical Transactions* (vol. 40, suppl., and vol. 41, p. 675). Many of the other early lectures were not published, though information concerning them is obtainable in the Royal Society Journal Book. We cannot here dwell on the other early Croonian Lecturers, as it would carry us far beyond the limits of an introduction, but a list of some of the early authors and titles is given below in the footnote.[27]

[25] Bernoulli, J. *Dissertatio physico-anatomica de musculorum motu.* Basle, 1694, 4°. *Meditationes mathematicæ de motu musculorum.* Leiden, 8 pp., 1710, 4°. These two were preliminary works. The following contains his important contribution in which he likens, as had Croone, the changes occurring in muscles during activity to the process of fermentation. *De motu musculorum, de effervescentia, et fermentatione, dissertationes physico-mechanicæ. Editio secunda priori emendatior; accedunt Petri Antonii Michelotti Tridentini animadversiones x. Ad ea quæ cl. vir Jacobus Keill M.D. protulit in tentamine v. quod est de motu musculari.* Venice: Typis Pinellorum Fratrum, 1721, 121 pp., 1 pl., 4°.

[26] Cowper, W. *Myotomia reformata: or, a new administration of the muscles of the humane bodies; wherein the true uses of the muscles are explained, the errors of former anatomists concerning them confuted, and several muscles not hitherto taken notice of described; to which are subjoin'd a graphical description of the bones; and other anatomical observations.* London: S. Smith, 1694. [xx] + 28 pp. The 2nd edition, 1724, contains an introduction concerning muscular motion by Richard Mead.

[27] 1738 Alexander Stuart. "On the Motion of the Heart, founded on some Anatomical Observations and Experiments." Phil. Trans., vol. 40, Supplement; vol. 41, p. 675.

1739 Frank Nicholls. "An Enquiry into Muscular Motion." Journal Book, vol. xviii, p. 70.

1740 Alexander Stuart. "Microscopical Observations on Several Parts of Live Frogs." Journal Book, vol. xviii, p. 290.

1741 James Douglas. "Description of the Several Muscles, Membranes and parts belonging to the Uvula of the Palate, and concerned in its action; as also of the several parts subservient to the uses of the Tuba Eustachiana." Journal Book, vol. xviii, p. 377.

We come now to the incomparable von Haller (1708–1777), the indefatiguable experimentalist and bibliographer. He has left us a wealth of material,—as extensive, in fact, as that found in any of our present-day encyclopedias of physiology. von Haller had apparently read and digested everything that had been written in physiology, as well as in medicine, anatomy and surgery. His volume on the physiology of muscle contains invaluable information concerning the work of the early muscle physiologists. He often refers to *theses*, and to work then in progress in other laboratories, which either were never published, or have completely disappeared. Monfalcon[28] has attempted to list all of von Haller's separate

1742 James Douglas. "Description and Structure of the Human Bladder, with the Uses of its Muscles and Membranes." Journal Book, vol. xviii, p. 419.

1744 James Parsons. "An Introductory Discourse on Muscular Motion." Phil. Trans., vol. 43, Supplement.

1745 James Parsons. "On Muscular Motion." Phil. Trans., vol. 43. Supplement.

1746 James Parsons. "Description of the Several Muscles of the Face; with their Particular Functions and Uses." Phil. Trans., vol. 44, part i. Supplement.

1747 Browne Langrish. "On the Theory of Muscular Motion." Phil. Trans., vol. 44, part ii. Supplement.

1750 James Parsons. "On Muscular Motion." Journal Book, vol. xxi, p. 357.

1751 James Parsons. "Critical Remarks upon the Motion and Uses of the Human Pelvis." Journal Book, vol. xxi, pp. 641, 652.

1777 to 1781 John Hunter. "On the Construction and Application of Muscles and the Power by which they are actuated." Journal Book, vol. xxxi, p. 194; and Annual Accounts, 1781.

1782 John Hunter. "On the Density and Firmness of a Muscle as contributing to its Strength and Agility." Journal Book, vol. xxxi, p. 194.

1784 Foart Simmons. "On the Irritability of the Muscular Fibres." Journal Book, vol. xxxi, p. 642.

1785 Edward Whittaker Grey. "An Examination into Haller's Theory of Muscular Motion." Journal Book, vol. xxxii, p. 259.

1786 Edward Whittaker Grey. "On the Effects of Different Kinds of Salts applied as Stimulants on the Muscles." Journal Book, vol. xxxii, p. 468.

1787 George Fordyce. "On Muscular Motion." Phil. Trans., vol. 78, p. 23.

1788 Sir Gilbert Blane, Bart. "On the Nature of the Muscles, and on the Theory of Muscular Motion." Journal Book, vol. xxxiii, p. 268.

1789 Sir William Blizard. "On the Theory of Muscular Motion." Journal Book, vol. xxxiv, p. 9.

1790 Sir Everard Home, Bart. "On the Mechanism employed in producing Muscular Motion." Journal Book, vol. xxxxiv, p. 200.

1791 Matthew Baillie. "A General View of the Nature of the Muscles, and an enumeration of the most striking facts connected with the Theory of Their Motion." Journal Book, vol. xxxiv, p. 419.

[28] Monfalcon, J. B. *Précis de Bibliographie Medicale*. Paris, 1827, 548 pp. (pp. 182–185; 452–462.)

monographs and contributions to scientific journals, and has given nearly 200 titles, but there are probably many more. His experiments were concerned with many phases of physiology, but his deepest interest apparently lay in the problem of irritability, one of his monographs on this subject alone occupying four volumes.[29] It contains admirable protocols of experiments and innumerable observations of extraordinary interest and importance.

In discussing the more general aspects of irritability, von Haller observed that the phenomenon was widely present both in the animal and in the vegetable kingdom and indeed appeared to be an almost universal property of living tissue. We cannot here enter into the nature of this argument for this has been dealt with at length by Foster (*334*) and by Daremberg (*220*). His contributions to muscle physiology and to the theory of contractility were extensive, as one will realize from reading the following quotation which is typical of von Haller's style and logical thought (*431*, pp. 46–48).

"But all the muscles are irritable. I do not know one that has not a natural palpitation after death; they all tremble, and are alternately contracted and relaxed. I have observed it in the temporal, pectoral, and sternocostal muscles, in the recti abdominis, cremaster, and sphincter of the anus. Dr. Whytt has observed the same in the sphincter of the bladder, and other anatomists in other muscles of the body. With regard to the sternocostals, I have often seen with pleasure, that upon cutting away the sternum, they still preserved a sufficient force to bend the cartilages of the ribs, and pull them inwards. The same muscles preserved their irritability a long time, nay even longer than the diaphragm. Farther, as the flesh in general of animals palpitates spontaneously after death, so it appears from an old experiment, which is known to every body, that this motion may be revived after the muscles have been some time quiet, either by irritating the nerve which goes to a muscle, or the muscle itself, with a knife, or corrosives. Dr. Zimmerman has made experiments of the same kind with mine, as also Dr. Woodward upon the muscles of oxen, Croone upon a muscle of the human thigh, and Bremond upon a frog; and Oeder observed the muscles to be violently convulsed upon being touched with salt. In making the former experiment it is of little consequence, whether the nerve is entire and communicates with the brain, or whether it has been cut through. In both cases the muscular fibre contracts, its extremities approach nearer to one another, and the succession of these motions represents a kind of undulation on the surface of the muscle. *On examining in a frog with a microscope the muscle thus convulsed, you do not see that the blood is pushed out; and it circulates as before.* There is no animal in which the muscles grow pale during their action, and I have long ago observed, that the paleness which Harvey said he had observed in the heart during its contraction, has been a source of errors into which the greatest men have fallen.

[29] A. von Haller, *Memoires sur la nature sensible et irritable, des partes du corps animal.* Lausanne: Bousquet (tom. i) and D'Arnay (tom. ii–iv), 1756–1760. This is a second and enlarged edition of that given in the bibliography below (*431*).

"In most part of the muscles the irritability is so great, that after one single irritation, the muscle contracts and is relaxed several times, by oscillations which diminish gradually, till they entirely cease. This alternate motion is very evident in the recti muscles of the abdomen, the sternocostals and others, where there is no difference in the direction of the fibres, which therefore Hamberger, and another author, had no manner of occasion to introduce into the structure of the heart, seeing the muscles just now mentioned oscillate perfectly well, though all the fibres are straight and parallel to one another. In the mean time Dr. Whytt is mistaken when he says, that this oscillation takes place in all the muscles, for it does not happen in the bladder, which after it begins to act, continues its contraction without interruption till all the urine is expelled."

Though Hooke, Steno, and Leeuwenhoek had observed recently excised muscle under the microscope, von Haller, as is evident from this quotation, observed intact muscle fibres microscopically during activity, and this was probably the first time such a procedure had been employed. In view of the recent advances in muscle physiology which have been made possible by the use of this method, its importance cannot be overestimated, and great credit is due to von Haller for having introduced it. von Haller's insistence that the local circulation in a muscle is not altered during contraction,—though possibly not strictly true,—is a point of much interest.

The question of "animal spirits" caused von Haller much perplexity. He pointed out that while the ancients postulated their existence, Swammerdam, Glisson and others had recently expressed grave doubts "about these spirits." He then discussed the matter dispassionately, collecting together all of the available evidence for and against the hypothesis.[30] He declined to regard nervous action as due to an intangible ether, such as Newton had postulated (*l. c.*, ¶ XV), and believed unlikely the possibility that nervous transmission was essentially an electrical phenomenon (*l. c.*, ¶ XV), as his contemporary, Fontana, had suggested. On the other hand, he noted that a nerve, following ligation, fails to swell proximally, even when stimulated above the ligature (*l. c.*, ¶ VII). Therefore the spirit which comes from the brain must be without sensible volume, "an element, too subtle to be grasped by any of the senses, but more gross than fire, or ether or electric or magnetic matter, since it can be contained in channels and restrained by bonds, and moreover is clearly produced out of and is nourished by the food" (*l. c.*, ¶ XVI).

Thus von Haller sanctioned the belief in animal spirits, but he defined in no uncertain terms the difficulties and limitations entailed by the adoption of such a view. von Haller's early view would thus harmonize with the

[30] *Elementa Physiologiæ*, 1766, vol. 4, Lib. X, *Cerebrum et Nervi*, Sec. VIII; the references which follow in the next few sentences of text refer to the numbered paragraphs of this volume, book and section.

humoral theory of nerve transmission by means of osmotically active substances, recently urged by Brinkman and von Szent-Györgyi (*156*).

An appreciation of von Haller's work and his methods will be found in the quotation from Foster at the beginning of this historical introduction. We may now consider von Haller's distinguished English contemporary.

Robert Whytt (pronounced "White") was the leading English physiologist of the eighteenth century. In a work entitled "An essay on the vital and other involuntary motions of animals," published in 1751, he defined the various attributes of excitable tissues, and on the basis of carefully-worded definitions, he proceeded to develop a theory of muscular action. In discussing the nature of an adequate stimulus, he appeared incidentally to be familiar with what we now refer to as the stretch reflex. He writes: "In proportion as the stimulus is more or less gentle, so (*caeteris paribus*) is the contraction of the muscle to which it is applied. *The motions occasioned by stretching the fibres of any muscle will be greater or less, as the muscle is more or less stretched; unless it be so far extended, as quite to lose its tone, and become paralyzed* [lengthening reaction?]. It deserves however to be observed, that the effects of different stimuli depend very much upon the peculiar constitution of the nerves and fibres of the muscles to which they are applied: Thus what will prove a stronger stimulus to the nerves of one part, will more weakly affect those of another, and vice versa." Whytt thus appreciated that the adequate stimulus for one nerve ending might not be adequate for another.

His book is filled with important observations on the characteristics of contraction in various muscles, and contains for the first time in the history of physiology a clear description of a reflex action (*1042*, p. 130). A brief account of a chapter from his book (*1042*) will give the reader an idea of the shrewd logic and exceptional insight of this brilliant man. Section X commences:

"Of the reason why the muscles of animals are excited into contraction by the application of a stimulus.

"The muscular fibres of animals are so framed, as to contract whenever a cause proper to excite their action is applied to them, or, in defect of this, always to remain at rest. This cause is either an effort of the will, or a stimulus of some kind or other: to the former are owing the voluntary motions; and to the latter all such as we call vital and spontaneous." He then proceeds to examine the various theories of muscular contraction put forward in the past. The elastic theory of Baglivi, he finds inadequate, because many elastic bodies exist which do not contract when stimulated. "Others," he goes on to say, "giving scope to a lively imagination, have

fancied the animal spirits lodged in the cavities of the muscular fibres, to consist of a number of little springs wound up, which, by the application of stimulating bodies, being put into vibratory motions, dilate these fibres, and so render the whole muscle shorter" (p. 231). In enumerating his objections to this hypothesis, he describes his beliefs in regard to animal spirits as follows: "But, waving the objection, that as the nature of the animal or vital spirits, as they are called, is altogether beyond our ken, every account of muscular motion from a *stimulus* which depends on their peculiar energy or manner of action, must therefore be merely hypothetical and precarious at best; may it not well be asked, why, if muscular contraction from a stimulus were owing to the animal spirits excited into an oscillatory motion, should pressing the belly of a muscle with a smooth body cause a weaker oscillation than the pricking of a pin, which is applied with less force, and affects only a very few of its fibres?" (p. 232).

In considering the objections to the next view, namely that contraction results "from some kind of explosion, ebullition or effervescence, occasioned by the mixture of the nervous and arterial fluids . . . . or from some very subtile ethereal, or electrical matter residing in the nerves," he brings forward the following telling arguments, and then mentions once more the pupillary reflex (by way of further argument) which has made his name ever memorable.

"If therefore muscular motion were owing to any of the causes above mentioned, it might reasonably be expected that it would only follow upon the application of certain kinds of stimuli to the muscular fibres: but we know from experience, that instruments of different metals, provided their sharpness and figure be the same, have an equal power of bringing the muscles of animals into action: that it makes no odds whether the stimulating substances be electrics *per se*, or non-electrics:—that acrid liquors of quite opposite natures have much the same effect, if their degree of pungency be equal: that acids, alkalies, neutral salts, heat, pricking, tearing, and in short every kind of irritation, excite the muscles of animals into contraction; and that there is no difference in the motions they produce, except what arises from their acting as stronger or weaker stimuli, *i.e.*, from irritating the part more or less.

"Further, no violent motion is produced by any bodies in nature, however active, unless the peculiar causes necessary to produce this be applied to them; but in order to the contraction of a muscle, it is not necessary that the stimulus should be applied to its fibres; it is enough that the common membranes covering them are irritated, the same effect being hence produced as from wounding the very fibres of the muscle. This is evidently the fact, in the case of the heart, stomach, guts, and bladder; *nay, many times muscles are excited into action by a stimulus affecting a remote part with which they have no immediate connexion, or so much as even a communication by means of nerves, unless it be that general one subsisting between all the parts, as their nerves are derived from the same brain.* Thus anything which affects the interior membrane of the stomach after a disagreeable manner, brings the diaphragm and abdominal muscles into convulsive contractions: *the action of*

light, as a stimulus, upon the tender retina is followed by the contraction of the orbicular muscle of the uvea, and according to the various impressions made by sounds upon the auditory nerves, the muscles of the internal ear are contracted variously" (pp. 236–238).

These, and other similar arguments published subsequently (1755), brought Whytt into conflict with von Haller. In regard to the experimental facts, there was singularly little difference of opinion between the two disputants. von Haller maintained that contractility was an innate property (*vis insita*) of muscle, existing quite independently of nervous influence, while Whytt urged that movement in normal organisms proceeds from an *unconscious* "sentient principle, which, in order to the getting rid of the pain or uneasy sensation of the muscle, determines the influence of the nerves into its fibres more strongly than usual." von Haller was clearly justified in his belief in independent contractility, and had convincing arguments to support them. Whytt, too, had ample justification for his postulates, but for a different reason. He had laid hold of the great principle that movements, under ordinary circumstances, originate reflexly from external stimuli, which often are not perceived by the individual. If, in place of "sentient principle," we substitute "spinal" or "reflex centre" in Whytt's work, it loses much of its eighteenth century flavour and becomes more strictly modern. von Haller focussed his attention largely upon the isolated muscle and saw that clearly; Whytt concerned himself chiefly with the reflex control of movement,— visualizing the organism as a whole.

THE RISE OF ELECTROPHYSIOLOGY

"Animal electricity," as the phenomenon was called when first observed, may be regarded as having been discovered through a chance observation of Galvani that frogs' legs developed spasms on being suspended by copper hooks from an iron ballustrade, the spasms occurring when the muscles came into contact with any part of the iron structure. This discovery, which eventually revealed to physicists the undreamed of powers of electricity, and to physiologists the more obscure electrical manifestations of living tissues, is too well known to require extensive repetition. Certain important details of the discovery, however, appear to have escaped the attention of the historians of science, and it is therefore permissible to draw attention to them in the account which follows.

It is evident from early papers in the *Bolognese Transactions* (see Mottelay, *726;* Dalton, *219*, Ch. I) that even before the year 1780 Galvani had made extensive observations on muscular contraction evoked by the discharge of static electricity (from Leyden jars, etc.). The experiments,

however, immediately concerned in the discovery of animal electricity were conducted during the summer of 1786. Galvani (1737–1798) and his good wife, Lucia, were endeavouring to test the action of atmospheric electricity upon frogs' legs during clear weather. On the 20th of September they observed what appeared to be spontaneous activity in their suspended frog preparations. Unfortunately we do not know who first noted the spasms, whether Luigi or Lucia. As Waller (*1017*) has remarked, it would be a question as to which of them first uttered "ecco," but this detail we

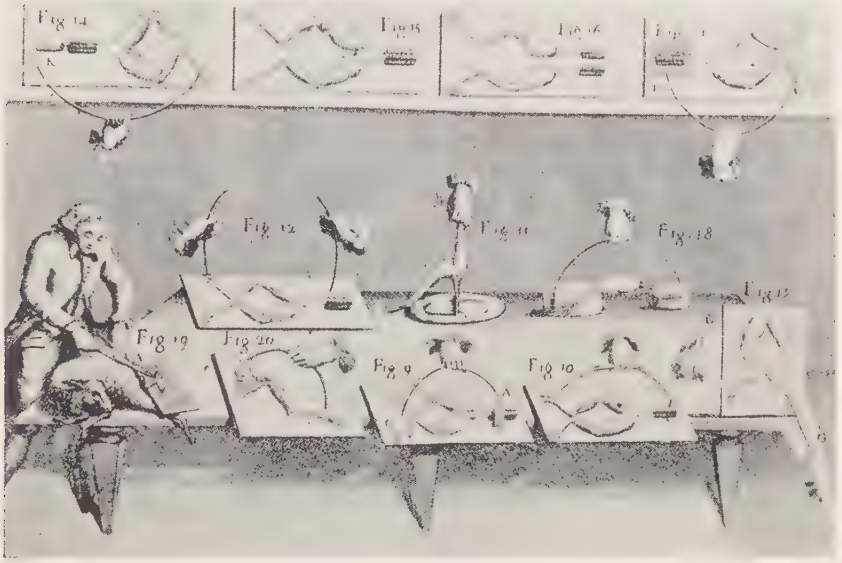

FIG. 9. A plate from Galvani's *De viribus electricitatis in motu musculari*, illustrating various experiments involving stimulation with dissimilar metals. Note that he examined the nerves of sheep as well as those of frogs.

shall probably never know. The phenomenon was promptly investigated and the results were eventually published in 1791 under the title of *De viribus electricitatis in motu musculari commentarius (374)*.[31] This contribution did not in itself prove the existence of animal electricity; as we now know, it merely showed that a muscle can be stimulated into activity by the

[31] It appeared first in the Memoirs of the Bolognese Institute of Science and Arts and 12 copies were published separately in the same year. In the following year a new edition appeared (1792) with annotations by Aldini (*375*) and a letter from Sig. Carminati adverting to Volta's objections to Galvani's experiment.

potential difference which results from the union of two unlike metals. The experiment has been carried down to modern times in the physiological classroom, and is still known as "Galvani's (first) experiment with metals." A reproduction of one of Galvani's plates is given in figure 9. It will be seen from this that he experimented not only upon frogs but on sheep as well.

Galvani's second experiment, without metals, proved the existence of potential differences in physiological tissues, but the circumstances relating to the second discovery are somewhat obscure. It will be recalled that the experiment consists in bringing the nerve of a nerve-muscle preparation into contact with an injured point of the muscle. The difference of potential between the nerve and the injured muscle stimulates the nerve and thus brings about contraction.

When Galvani's contribution was first published it provoked a storm of criticism from his fellow countryman, Alessandro Volta (1745–1827), Professor of Natural Philosophy at Pavia. Galvani had contended that contraction in his (first) experiment resulted from "animal electricity" being conducted by the metal, while Volta objected quite rightly that the conclusion did not follow from Galvani's observations; Volta maintained, on the contrary, that the stimulation resulted from the electricity which was generated by contact of dissimilar metals. There is no question but that Volta was justified in his criticism. Its adverse nature led Galvani (or his nephew, Aldini) to demonstrate conclusively the possibility of contraction without metals. This experiment was probably first performed in 1793, but the results were not published until 1794. They were described in an anonymous tract entitled "Dell' uso e dell' attivita dell' arco conduttore nelle contrazioni déi muscoli" (*376*). Who was the author of this "Trattato"? In a subsequent essay, Aldini (*23;* 1803) referred to the experiment as his own. Yet Gerhardi in The Collected Works of Galvani, published in Bologna in 1841, attributes the "Trattato" to Galvani, as does also du Bois-Reymond (*121*). Aldini was then Professor of Physics in the University of Bologna and was living in his uncle's house. Aldini's subsequent accounts of the early observations provide ample evidence that he must have been present at the majority of his uncle's investigations, and he undoubtedly made many suggestions in the course of the work. Possibly he suggested the experiment without metals, but there can be little doubt that the first description was given by Galvani himself in the anonymous "Trattato," for the manuscript which was at one time preserved in the University Library at Bologna has been described as being largely in Galvani's handwriting. This we must take on the evidence of du Bois-Rey-

mond, who obtained information concerning the manuscript in 1848. Unfortunately it has now disappeared and its recovery would probably be the only way in which the question could be finally settled.

We have here an example of two supremely important discoveries which arose from a controversy. Galvani had asserted from the beginning the existence of animal electricity, but he denied that of metals. Volta, on the other hand, disallowed the existence of animal electricity and asserted that of dissimilar metals. It is now evident that both assertions were correct, and both denials incorrect (Waller). "Animal currents exist, metal currents exist; the latter in Volta's hands were the seed out of which have sprung the battery, the telegraph, the electric motor, the electric light, and the telephone; the former in Galvani's hands is the parent of the more hidden offspring, animal electricity, or the electricity evolved by living tissues." No impartial judge of the history of science can regard Galvani and Volta as equals. Volta was endowed with the rare gifts of perseverance and scientific imagination, while Galvani, though he had great perseverance, seldom saw beyond the horizon.

The announcement of the discoveries of Galvani and Volta led to an intellectual outburst which can only be compared with the political upheaval of the time. One finds in the literature of the period from 1791 to 1798 no less than fifty separate titles of contributions to the subject of animal electricity (*e. g.*, *173*, *996*).[32] As du Bois-Reymond has remarked, wherever frogs were found and where dissimilar metals could be obtained, everybody attempted to see how the mangled limbs of the frogs could be once more brought to life. Visions were entertained of new vital forces and powers, and one can judge of the importance of the discoveries by the rich fruition of knowledge to which they eventually led.

In the later stages of the history of animal electricity little progress was made owing to absence of instruments for measuring electrical currents. Volta, being, as we have said, undoubtedly a greater scientist than Galvani, had inspired greater faith in the world at large, and with the death of Galvani in 1798 there seemed little doubt but that the views of Volta would triumph. But late in 1797 appeared an extraordinary work by that versatile descriptive naturalist, Friedrich Heinrich Alexander von Humboldt who examined critically the views of Galvani and Volta and recorded a large

[32] References to many of them are given in von Humboldt's book (*506*, 1797). An extensive list is also to be found on p. 427, vol. ii, of Thomas Young's *Lectures on Natural Philosophy* (London, 1807). Bostock's *History of Galvanism* (*130*, 1818) also gives useful references. Consult "Electricity, Animal" and "Muscle, Electric Phenomena of" in the *Index Catalogue* of the Surgeon-General's Library.

number of experiments performed upon a great variety of animals. He gives the following summary of his results (*506*): "Thus I have excited vivid muscular contraction, (1) by bending the thigh of an animal upon its sciatic nerve when these parts were in organic connection; (2) by touching simultaneously the crural nerve and the muscles of the thigh to the portion of the crural nerve which had been cut off [contraction without metals]; (3) by establishing a circuit between one point in the nerve and some other point of the same nerve by means of some animal tissue." In addition to this von Humboldt also showed that under special circumstances contraction may result from contact of homogeneous metals. Thus he says, "It is indisputably true and is proved by the observations of the great Ticinian natural philosopher that when an animal is not convulsed when touched by homogeneous metals it may be so affected when the metals are made heterogeneous by the slightest alteration in mixture, polish, hardness, form, or temperature." von Humboldt was thus the first to take an intermediate position in this bitter controversy, but his conclusions were not adequately recognized for more than forty years. This is largely due to the fact that in 1799 Volta discovered the battery which made his name memorable for all time. Owing to this, his previous opinions on many subjects gained complete victory, and animal electricity was for the time being forgotten.

In 1811 Schweigger had devised the first galvanometer, but not until Oersted's (1821) discovery of the deflection of needles surrounded by a current-bearing solenoid was an accurate galvanometer possible. The first attempt to use a galvanometer for the measurement of animal electricity was made in 1827 by Nobili (*735*), who two years previously had discovered the astatic needle galvanometer. He came to the conclusion that while electric currents were to be obtained in frogs' muscle, the origin of this current was probably "thermo-electric," *i.e.*, he ascribed it to the more rapid cooling of the nerve in relation to the muscle. Owing to the curious interpretation which Nobili placed upon his observation, the existence of animal electricity was not again established until 1838, when Carlo Matteucci (1811–1868) published his experiments on the frog current.[33] As Bence-Jones points out, Matteucci chiefly deserves credit for having established that a difference of potential does normally exist between an excised frog's nerve and its (damaged) muscle. He was also the first to introduce the word "tetanize."

The early history of animal electricity is thus entirely concerned with

[33] The original paper on the frog current was reprinted in Paris in 1840, unchanged and without addition, in Matteucci's "Essai sur les Phenomenes electriques des Animaux" (Ch. 6, part 2).

the demonstration of the existence of what we now call the "current of injury."

The greatest name in the early history of electrophysiology is that of Emil du Bois-Reymond (1818–1896) of Berlin. Though of French extraction he wrote almost entirely in German and with that clarity and finesse so often associated with the French mind. A pupil of Johannes Müller, he succeeded the latter as Professor of Physiology in 1858. Early in his career he attacked the problem of the nerve-muscle preparation and, as he records (*121*, vol. 1, p. v), was introduced to the subject when Müller handed to him in 1841 the then recently published paper of Matteucci. du Bois-Reymond's studies in this field were published in a voluminous work, the first volume of which appeared in 1848 (*Thierische Electricität*).

du Bois-Reymond introduced faradic stimulation by means of make and break shocks of the induction coil which is called after him (*121*, Bd. 2, 1849). He also introduced the so-called "du Bois key." His exhaustive investigation of physiological tetanus laid the foundations for our modern conceptions of summation of response and prolonged contractions. He was the first to describe "electrotonus," and the conditions of enhancement and depression of excitability characteristic of this condition, he represented graphically by means of algebraic curves. In this way he paved the way for Pflüger's (1829–1910) elucidation of the "law of excitation" (*770*). du Bois-Reymond in addition made the important observation that a tetanized muscle produces an acid while the resting muscle is "neutral" in its chemical reaction. He also pointed out that a constant current has no effect upon a nerve and that the necessary factor for stimulation is a changing potential. It would be out of place in such an account as this to give a description of du Bois-Reymond's extramural activities. It will suffice to say that he was a man of wide interests and broad philosophical outlook.[34]

The discovery of the negative variation or action current. The early observations upon animal electricity, as we have seen, proved only the existence of the "current of injury." Matteucci (1840–1841) had observed that the "muscle current," as the injury current was then designated, becomes diminished during a tetanic response, but, as Bence-Jones points out (*68*, p. 127), Matteucci later contradicted himself (1844) by saying that resting "muscle current" is increased during stimulation; finally he denied (1847) that activity had any effect upon the "muscle current," and attributed his former results to technical errors. Matteucci made the important discovery, however, of *secondary contraction*, which he first announced in February of 1842 (*693*). When the nerve of one limb of a frog is placed upon the muscle of a similarly prepared limb, the first limb will contract whenever the muscle of the second limb is caused to contract. Becquerel

[34] For the details of du Bois-Reymond's life I am indebted to Boruttau's short biography (1922), and to Garrison's *History of Medicine* (*380*).

attempted to explain this result by assuming that the contracting muscle must give rise to something akin to an electric discharge which stimulates the rheoscopic nerve, thus causing contraction. This was of course close to the truth, and while Matteucci was at first favourably inclined toward Becquerel's explanation, he subsequently abandoned it (1845), and attempted to show that "induced" or secondary contractions are not electrical in origin but rather the result of "nervous forces" in the primary muscle.

Though Matteucci undoubtedly observed negative variations in some of his experiments, he cannot be regarded as their discoverer. This we owe to du Bois-Reymond. In his first contribution to the subject of animal electricity in 1843 (*120*) du Bois-Reymond observed that the current of a resting muscle becomes diminished during tetanic stimulation; in other words the "current of rest" undergoes a "negative variation." For this reason the current denoting activity came to be called the negative variation. du Bois-Reymond made a detailed investigation of the phenomenon, the results of which were described in extenso in 1848 (*Thierische Electricität*, Bd. 1, *121*). In this he proved that the negative variation does not arise fortuitously from movement of the muscle beneath the electrodes, and by a series of ingenious experiments demonstrated that it was not due to an alteration in the resistance of the muscle itself. He proved also that negative variations occur in nerves. From that time on the negative variation, or "action current" as it was later called, was regarded as the usual concomitant of contraction of muscles and of the impulse of nerves. Further historical details are to be found in Bence-Jones' *Animal Electricity* (*68*).

The controversy concerning the nature of the injury current of resting muscles ("Demarcation" current). du Bois-Reymond held that "currents of rest" are to be found in quiescent muscles at all times and that injury of the muscle simply augments or unmasks them. To him a muscle or a nerve was to be regarded as a series of bipolar electromotive molecules, with definite positive and negative surfaces, arranged in regular fashion in an electrically indifferent ground substance. The middle of a strip of nerve, as a result of this internal arrangement, is "positive" (galvanometrically) to the two ends (which are "negative"), the diminution during activity of this resting potential difference between the longitudinal surface and the transverse ends constituting the negative variation.

Hermann (1838–1903), on the other hand, insisted that when adequate precautions are taken to prevent injury during exposure of the muscle, all points along its surface are isoelectric (*463*, Bd. 1, p. 235); in other words, there is no current of rest in an uninjured muscle. According to Hermann, electromotive forces are absent in muscle until they are called into existence

by chemical changes occurring at the "plane of demarcation" (*i.e.*, the boundary) between sound and injured tissue. Injury currents, which du Bois-Reymond had called "currents of rest," were accordingly designated by Hermann "demarcation currents." When two careful experimenters disagree on a fundamental point, it seldom happens that one is right and the other wrong, the truth, as with Galvani and Volta, usually lies in a middle ground, and this was clearly the case with Hermann and du Bois-Reymond. Hermann was correct in his contention that differences of potential do not exist along the longitudinal surface of uninjured resting muscle, and consequently he was justified in discarding the term, "current of rest," as inadequate, but he was clearly incorrect in his assumption of the absence of a pre-existing electrical equilibrium between surfaces within the individual fibres.

The more modern conceptions of the origin of bio-electrical currents introduced by Bernstein (1839–1917) and by J. S. Macdonald (*671, 672, 673*), lead us directly back to du Bois-Reymond's conception of a surface of regularly oriented electromotive "particles." As Stewart points out (*971*, p. 829), if we but substitute electrically charged ions and the semipermeable membrane for du Bois-Reymond's surface of positive and negative "electromotive particles," we have the essence of the modern physico-chemical theory. There is now little doubt but that electrical manifestations of living tissues result from ionic concentrations at "interfaces" within the cells. When the tissue is injured these electrically charged ions migrate freely from the normal to the injured area, thus setting up a new distribution of charges or a potential difference ("injury currents"). Bernstein (*91*), Brünings (*172*), and Beutner (*98–101*) have compared injury currents of muscle to the potential arising between solutions of the same electrolyte at different concentrations when separated by a "fatty" interface (Cf. Bayliss's Textbook, *59*). When, owing to stimulation, the permeability of the internal interface is altered temporarily, an electromotive disturbance is set up, and this constitutes the action current. A further elaboration of this, the "modern" theory of animal electricity, will be found in the course of the following chapters.

The early observations on electrical responses were made with the astatic needle galvanometer. The capillary electrometer, which was designed by Lippmann in 1872, considerably enhanced the accuracy of the observations in action currents, especially as used by Burdon Sanderson (1828–1905) and Gotch (1854–1913; see *182*).

Recent advances in electrophysiology of muscle have been made possible through the introduction by Professor Willem Einthoven (*268*) of Leyden, of the string galvanometer which bears his name. The high sensitivity of this instrument together with its relative

absence of inertia has enabled scientific investigators to discover the chronological relations of electrical and mechanical activity with approximate exactitude. In the hands of Sir Thomas Lewis (*629*) and others this instrument has led to a series of brilliant discoveries in the realm of cardiac physiology and pathology. Within the last few years the development of the triode valve has made possible the perfection, by Gasser and Erlanger, of a cathode ray oscillograph (*386*), an inertialess electrical recording system by means of which the action currents of nerves have been placed without distortion under direct observation. Though muscle action currents have not yet been examined by this method, the oscillograph will undoubtedly lead to a great clarification of the problem when it is used.

THE HISTORY OF THE THERMODYNAMICS OF MUSCLE

We have seen that it was stimulation of muscle in the hands of Galvani and Volta that led to the great discovery of galvanic electricity, and it is interesting to find that muscles were used again by von Helmholtz (1821–1894) in paving the way for another equally important contribution, the first law of thermodynamics. Contact with Johannes Müller (1801–1858) had led the searching mind of the young von Helmholtz to consider the problem of energy transformation in physical and chemical systems. His clear vision led him at once to formulate the great issue of the energetics of vital phenomena. Is there, as Johannes Müller so devoutly believed, a vital, energizing force which is not susceptible to the chemical analyses that Liebig was then performing, or is the problem of vital force one purely of the energetics of inanimate systems? With this before him, von Helmholtz was led to experimentation upon the muscles of "that ancient martyr to science," the frog.

A word may be said concerning von Helmholtz's early training. Born in 1821, he came at the age of 18 to the laboratory of Müller, and he soon found himself enamoured both of the good professor and of his subject. He commenced work a year later on his thesis, which was eventually accepted in 1842. It was entitled "*De fabrica systematis nervosi evertebratorum*" (*451*). In this work he established for the first time that the axons of peripheral nerve fibres are connected with ganglionic nerve cells, and in this way he proved the central origin of nerve fibres.[35]

In 1843, the year after the publication of his thesis, his paper on the nature of fermentation and putrefaction made its appearance (*452*). It is interesting to realize that he correlated putrefactive processes with the presence of organisms and pointed out the striking resemblance between vital processes themselves (their rate of growth and optimal conditions of

[35] *Hermann von Helmholtz*, Leo Koenigsberger, Braunschweig: Vieweg, 3 Bd, xii + 375, xvi + 383, x + 142 pp.

activity) and the putrefactive process. But despite the great promise of this first contribution, he was soon diverted into other fields and the problem was left for Pasteur. In the course of his work on putrefaction he had become convinced that the notion of a vital force should be abolished from all physiological conceptions and that the only avenue of progress to physiological knowledge was through physics and chemistry. This idea dominated his mind and led him to study for himself the more abstruse problem of the nature of energy and matter. It is recorded by his biographer[35] that he never attended a mathematical lecture, yet, when at the age of 26 (1847) he communicated his epoch-making paper on the conservation of energy, he proved himself an accomplished master of mathematical science. In fact, he had no peer.

By 1844 the conception of the conservation of energy occupied his mind unremittingly and he finally turned to physiology for his experimental proof. He now asked himself more specifically whether the mechanical energy and heat produced in muscle results entirely from its own metabolism, or whether it arises *de novo* from the mysterious vital processes. To examine the question von Helmholtz set out to investigate the chemical transformations occurring in frog muscle during activity (*453*). He stimulated the gastrocnemius muscle through its nerve by means of a static machine and a Leyden jar and was able to demonstrate that a chemical transformation does occur, and he compared the chemical process to that which he had described as characteristic of fermentation and putrefaction. He spent little time in detail, and the descriptions of his results were ever simple and direct; yet he realized that to prove his point as to the indestructibility of energy he must determine the relation of muscular activity to its heat production. This required a fresh series of experiments with a new apparatus.

While preparing this he occupied himself with an historical review of the physiology of temperature regulation in the animal kingdom, attempting to elucidate the origin of animal heat (*454*). He urged that since energy can neither be increased nor diminished in nature the quantity of heat must similarly remain absolutely constant, and he concluded that since the temperature of an animal cannot be due to the heat of its environment (free or latent), animal heat must necessarily be derived from the combustion of food. von Helmholtz emphasized the fact that the only alternative to this conclusion was the assumption of special vital forces.

His investigation on the heat production of muscles was sent to Müller's Archiv in 1847 and published early in the following year (*456*). Employing the Becquerel thermocouple with a triple junction of iron and German silver

wire with every precaution to exclude extraneous temperature alteration, he was able to demonstrate a rise of temperature during contraction. This he attributed to the chemical break-down which he had previously demonstrated in active muscles. von Helmholtz's thermocouple, the first

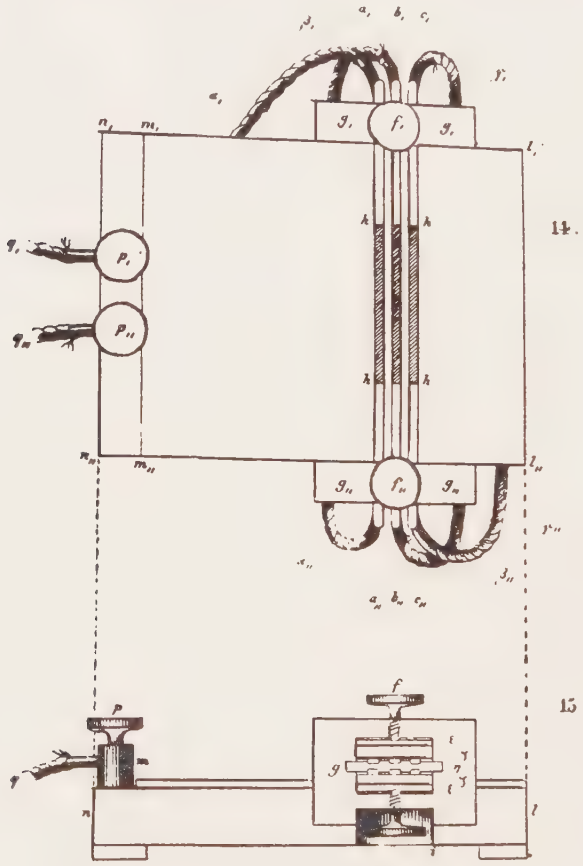

FIG. 10. von Helmholtz's diagram of the thermocouple which he used in establishing that isolated frog muscles liberate heat when thrown into activity. It was a triple junction of iron and German-silver wire, the first ever used in a physiological research. (From *Müller's Archiv*, 1848, Taf. 6.)

ever used for studying the heat production in muscle, is reproduced in figure 10. Experiments on nerve proved entirely negative, and it is interesting that even with the most delicate of modern apparatus the magnitude of the heat production of nerve is so minute as still to remain problematical. The

data which von Helmholtz obtained in this way were not extensive nor perhaps even conclusive, but they nevertheless were all in harmony and thus tended to verify his law.

In 1847 he published his memorable work on the Conservation of Energy (*455*). We cannot deal here with the importance of this contribution or with the more difficult matter of priority. Robert Mayer (1845) and Joule both had earlier claims, but no one can doubt but that it was the genius of von Helmholtz which unified and generalized the conception and brought it to the attention of the scientific world. He expressed himself with greater clarity and assurance than had Mayer or Joule, and it is clear that von Helmholtz evolved the conception quite independently of them.

It would be interesting to follow the further details of von Helmholtz's physiological experiments, but it would carry us away from our subject. If their simplicity and directness does not surprise us, when we consider the prolixity of his contemporary fellow countrymen, they at least require our perpetual admiration. When he had proved a point, he left it for others to elaborate the details and proceeded himself to new and intriguing problems, as if life were not long enough to accomplish all that he would like to do. We cannot dismiss von Helmholtz, however, without mentioning his classic experiment upon the rate of conduction of the nerve impulse (*457*). No sooner had he finished the experiments on heat production than he threw himself into this new problem. A few years previously (1844) Pouillet had found that small intervals of time could be measured accurately by the deflection of a ballistic galvanometer needle (the smaller the deflection the more brief the current), and Helmholtz elaborated the method for his experiments on nerve. The stimulation circuit of the nerve served to close the galvanometer circuit, and the first movement of the muscle was arranged to break a contact which opened the galvanometer circuit. When the nerve was stimulated at a distance of 5 cm. from the muscle the deflection was considerably higher than when stimulated at 1 cm. from the muscle. This gave evidence of the time required to traverse the 4 cm. of nerve, and by this, again simple, method he proved, on the one hand, the existence of a latent period of contraction of muscle and, on the other, established that the nerve of a frog conducts impulses at a rate of 27 to 30 meters per second. In 1851 von Helmholtz published his description of the ophthalmoscope (*458*). It is doubtful whether anyone in the course of five short years of life ever made more substantial or more varied contributions to knowledge than did von Helmholtz between the years 1846 and 1851.

For many years von Helmholtz's observations on heat production of muscle remained the only ones in this field. Heidenhain (*450*), however, in 1864 set out to determine the amount of heat produced by a given contraction and attempted to correlate heat production with other phenomena of the excitatory state. It will be remembered that the work of Joule (who published in 1842 and 1850) was practically contemporary with that of von Helmholtz, who consequently was not in a position to employ Joule's results in determining the mechanical equivalent of heat. Heidenhain, however, was able to take advantage of Joule's work. Heidenhain investigated the effect of stimulus intensity upon heat production. He was able

to determine that the thermal response varied with the stimulus in the same way that work varies, but he also observed that the increase in the production of heat which results from raising the stimulus intensity is more than would be proportional to the greater work done. Other details of Heidenhain's investigations will be found in Burdon Sanderson's chapter in Sharpey-Schafer's Text-book (*181*).

The next important contribution to the problem of heat production was that of Fick (1829–1901). In a detailed investigation, which occupied many years of continuous work, he was able to correlate the mechanical conditions of contraction with heat liberation. He made the important observation that heat production increases with the initial length of the muscle fibres. He also found that the quantity of heat referable to each excitation of a tetanus varies almost inversely with the rate of stimulation (Cf. Hill, *472*). The chronological relations of the mechanical and thermal responses of muscle were studied by Fick, but his observations did not lead to a clear differentiation of the phases of heat production which, as a result of the investigations of A. V. Hill, we now know to exist. Fick's greatest contribution, however, was his demonstration that chemical energy in the case of muscle is transferred directly into work without passing, as in a thermodynamic machine, through an intermediate stage of heat. Engelmann (*280, 281*) had put forward the view that muscular contraction is caused by the evolution of heat at microscopic foci within the fibre, and that this local enhancement of temperature gives rise to shortening of the doubly refracting surfaces of the fibres, just as heat causes catgut (which is also doubly refracting) to shorten. In a carefully developed argument, drawn largely from the second law of thermodynamics, Fick showed that Engelmann's view is inadequate and that muscle is to be regarded as a mechanism in which chemical energy is, as has been stated, transformed directly into work. Any heat which happens to be evolved, he urged, is probably incidental to development of tension and change in shape. This fundamental conception has profoundly influenced the development of muscle physiology (see especially, Bayliss, *58*). Its immediate effect was to stimulate interest in the nature of the chemical processes underlying energy liberation.

Fick also demonstrated the value of precise mechanical records. His tension lever marks an important step in the development of physiological knowledge. Later Magnus Blix (*105*) obtained synchronous records of isometric and isotonic contractions and was enabled in this way to compare these two important phases of muscular activity. Accurate graphic methods were, however, developed with pre-eminent success by Étienne Jules Marey (1830–1904) In his important book, "La methode graphique," he worked

out the physical principles of a large variety of different recording systems and described the results to be obtained and the limitations of each method. This monumental contr bution, though it has been superseded in certain practical details, still remains a classic work on the theory of graphic recording. A further important contribution to the art of graphic recording has lately been made (1921) by Sherrington (*932*) in the perfection of his optical torsion-wire lever (see Appendix of the present work), with the technique of its use for intact muscles of mammalian preparations.

Chemical transformations in muscle. Though the work of Fick stimulated new interest in muscle chemistry, it must not be assumed that previous workers had not already attempted to unravel these processes. We have already seen that John Mayow (1645–1679) had suggested that muscular contraction was made possible through the interaction between the salts of the muscle and a substance carried by the blood. In 1800 Richerand (1779–1840) suggested that nervous influence (*805*, p. 311) causes the splitting of chemical bodies which in turn "activate" the muscle fibres. He attributes this theory to the German chemist, Girtanner (1760–1800), who looked upon swelling, shortening and "induration" as due to the "splitting" of certain chemical elements contained within the muscle fibre, and he believed that they were (subsequently ?) oxidized by the arterial blood. Spallanzani (1729–1799) had observed that living tissues continued to yield carbon dioxide long after their oxygen supply has been cut off,—an observation confirmed by Müller, Liebig and Matteucci (*694*). Hermann (*462*), who also obtained this result, made it the basis of his theory of the "inogen" molecule. According to him, inogen was the precursor of both lactic acid and carbon dioxide. It was supposed that after break-down of this molecule restorative powers in the muscle led to a recombination of lactic acid with other carbon-bearing molecules, to form once more the inogen precursor (see Fletcher and Hopkins, *309*). Pflüger (1829–1910) accepted the inogen hypothesis and made the further assumption that this giant molecule also contained intra-molecular oxygen, which facilitated respiration in the absence of an external oxygen supply. The problem was taken up at the end of the nineteenth century by a large number of investigators. Gad (*371*) was probably the first to suggest specifically that lactic acid caused contraction and that it was subsequently oxidized with the liberation of heat,—the heat of "oxidative recovery," as it is now called. The most significant contributions, however, were those made some years later by Fletcher (*306*) and by Fletcher and Hopkins (*308*). The mystery of the inogen molecule was put aside, and it was demonstrated conclusively: that lactic acid owes its origin to glycogen, that when lactic acid appears glycogen invariably disappears in corresponding quantities, that carbon dioxide is evolved from

the neutralization by preformed carbonates of the lactic acid set free, and finally that these processes of liberation and neutralization occur in the complete absence of oxygen. The oxygen subsequently utilized serves to oxidize carbohydrate and is not stored as intra-molecular oxygen. The change of outlook was thus complete (Hill), and we are now able to look upon the process of lactic acid formation in muscle as one whose fundamental aspects have been settled, almost beyond the peradventure of doubt.

THE "ALL-OR-NONE" THEORY AS APPLIED TO MUSCLE

Early physiologists quite naturally attributed gradation of muscular response to variations in the intensity of stimulation. Many inferred, however, that a strong stimulus sets up a large response because it gives rise to "larger" nerve impulses and to larger contractile responses than a weaker stimulus. In recent years the alteration of this belief has also been complete and decisive.

H. P. Bowditch (*140*) discovered in 1871 that the traditional view did not hold in the case of heart muscle, for a stimulus, if adequate at all, caused the heart to respond to its maximum extent. Further increase in the stimulus intensity did not provoke a greater response. Marey (*686*) had observed that the heart was continuously excitable in diastole and refractory during the greater part of systole, and Bowditch emphasized that during diastole any stimulus which was adequate evoked a maximal response. It was, in truth, an "all-or-none" affair.[36] Bowditch had worked in Ludwig's laboratory with Krönecker. Krönecker had been associated with Bowditch in early experiments, but he refrained from adding to the experimental evidence until 1874, when he too reported similar results which amply confirmed and considerably extended (*559*) those which Bowditch had originally reported. It was tacitly assumed, however, that the reason why the response of the heart behaved in this way was due to the spreading of the excitation from fibre to fibre. It is well known that the cardiac fibres are not insulated from one another, as in the case of skeletal muscle, and the early conception of a variation in size of individual fibre responses with the alterations of stimulus intensity continued to be held for skeletal fibres. Certain writers, notably Fick (*303*), had expressed doubt concerning the interpretation, but offered scant experimental evidence to substantiate their convictions. Fick (*303*), however, made this interesting observation: "Each impact of excitation discharges either a maximal contraction or no contraction at all; it is only in a limited interval in the scale of excitation (often hard to find on account of its narrow proportions) that *sub*-maximal, so-to-say, imperfect contractions are given." (See Biedermann, *103*, i, p. 69). Fick was thus on the verge of grasping the all-or-none conception, but being more interested in the thermodynamics of muscle, he did not fully appreciate the significance of his observations.

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[36] Certain writers of text-books have referred to this as the "all-or-*nothing*" principle. As those who have made original contributions to the subject have used the term "all-or-*none*," it seems preferable to preserve that terminology.

Early in the present century Gotch (*406*) made the important observation that nerve fibres appeared to give all-or-none responses. He (in collaboration with C. G. Douglas) observed that when one of the lumbar roots supplying the gastrocnemius muscle (frog) was stimulated, a certain proportion of the muscle fibres remained unstimulated and could be called into activity by stimulation of the other root. In view of this, and other evidence based upon the time relations of the action current, he suggested that gradation of muscular response was brought about through variation in the number of contractile units in activity at any one time rather than through variation in size of the nerve impulse. He remarks also, that "as regards

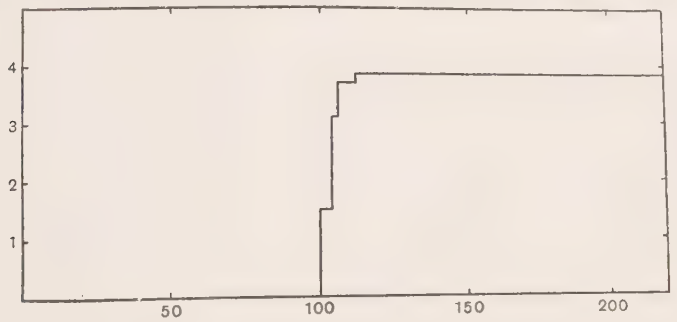

FIG. 11. Keith Lucas's diagram showing the discontinuities in contraction amplitude of the dorso-cutaneus muscle of the frog as the intensity of stimulation is gradually increased. Ordinates = isometric tensions; abscissæ = intensities of stimulus. (*Journ. Physiol.*, vol. 38, p. 113.)

both muscle and nerve, the obvious gradation in the intensity of active effect dependent upon intensity of stimulus is mainly due to these tissues being composed of a large number of elements having no physiological continuity with each other."

The hypothesis of Gotch received strong support from the ingenious experiments of Keith Lucas (*661*). He found in such a muscle as the cutaneous dorsi of a frog, which is innervated by a small nerve containing only 7 to 9 fibres, that the degree of the contraction of the muscle increases in steps as the intensity of stimulation applied to the nerve is gradually increased (fig. 11), and that the number of steps is never greater than the number of nerve fibres supplying the muscle (*i.e.*, 7 to 9). Lucas suggested, in view of this, that the extent of the tension development varied, as Gotch had supposed, with the number of muscle fibres stimulated. He found, moreover, that after all the fibres had been called into activity by a stimulus of gradually increased intensity, further increase did not augment

the extent of the contraction. Veley and Symes (*998*) and Mines (*717*) similarly observed in responses of sartorius stimulated through nerve filaments, in which the number of functional constituents had been reduced, that the contraction tension increased with stimulus intensity in a limited number of abrupt steps. The evidence from these experiments was extremely suggestive, and led many physiologists to readjust their views concerning the nature of the process underlying gradation of activity in muscle (Stiles, *972*, Barbour and Stiles, *53*). It is true, nevertheless, that the experiments of Lucas and others did not provide *direct* evidence of the all-or-none character of the response of muscle fibres, for each fibre itself "might be discontinuously graded." Such evidence could only be provided by direct observation of the contracting units, and it remained for Pratt (*780–784*) to make this far-reaching contribution.

In a series of experiments of great ingenuity, Pratt demonstrated the all-or-none behaviour of individual muscle fibres by direct observation under the microscope. Employing a pore electrode of somewhat smaller diameter than that of an individual muscle fibre, he was able to show that once a fibre had responded further increase in the stimulus did not make it contract further. This he proved by sprinkling fine droplets of mercury on the surface of the muscle and photographing the extent of the excursion of a droplet situated over a single active fibre. The aims and general results of Pratt's work are best given in his own words (*781*, p. 520):

"It was the need of thus assuming one or the other of the two views of graded muscle function, in interpreting certain fatigue phenomena, that led me several years ago to attempt a study of localized response in skeletal muscle, disregarding for the time the suggestive bearing of the principle of all-or-none nerve fibre activity, foreshadowed by Gotch and in recent years so convincingly supported, especially by Adrian. The problem of method was to observe directly, and, if possible to record, the response of muscle fibres, single or in distinguishable groups, in the hope of obtaining data leading to similarly direct conclusions as to the jurisdiction of the all-or-none law, if such be found to obtain. Cumulative results by various methods have shown with consistency that magnitude of quick response in skeletal muscle is independent of magnitude of stimulus, except in so far as discrete quantities of effect suddenly appear or disappear at appropriate levels of a graded excitatory influence. A fact of related import has also been established; magnitude of uniformly induced contraction in the fibre is constant through appreciable ranges of threshold value."

Pratt and Eisenberger (*784*) demonstrated that the excursion of a droplet of mercury placed on the region of the muscle to be excited increased in steps as the strength of current was gradually increased, and that, on the other hand, when the strength of stimulus was decreased again the contractions fell off in the same series of steps. This is shown in figures 12 and

13, taken from the paper of Pratt and Eisenberger (*784*). It may be emphasized that the photographically recorded discontinuities in the extent of the excursion of the mercury droplet were not merely *inferred* to represent added fibres, for they actually observed through the microscope that added fibres *were* brought into play when these steps occurred. It is evident from observations with pore electrode stimulation that each individual fibre in a muscle must be "insulated" from the others so that one can contract without involving the others. If this were not so, delicate gradation of movement would be impossible, and skeletal muscle would, owing to the spreading of the excitation wave, always contract *en masse*, just as does the heart.

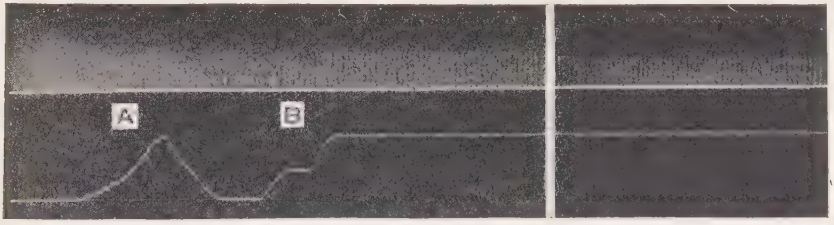

FIG. 12. One of Pratt and Eisenberger's (*784*) figures, showing the deflection of a mercury droplet on the surface of the sartorius muscle of a frog stimulated with successive break shocks by a pore electrode 7μ in diameter. The "quantal" deflection is presumably caused by the contraction of a single fibre, the larger excursions by 2, 3, or 4 fibres, etc. The lower line indicates the gradual movement of the secondary of an inductorium in the direction of increased intensity. Note the abrupt incremental transitions in size of the deflection, as contrasted with the gradual alteration in intensity of stimulus. Never were intermediate steps observed. Fibre fatigue developed in the course of the response as is evidenced by the smaller size of the second part of the record, 134 responses having intervened between the two. (From *Amer. Journ. Physiol.*, vol. 49, p. 44.)

Though a skeletal muscle fibre contracts to its utmost, if it contracts at all, it is not to be supposed "that under all circumstances maximal contraction is of the same magnitude" (Redfield, *798*). Other factors, such as the initial length of the fibres, the mechanical conditions which obtain in the course of the response (Fenn, *298*, p. 200), and the staircase effect (*i.e.*, the previous history of muscle), all modify the ability of the fibre to develop tension. This will be referred to again in Chapter IX when discussing certain of the objections which have been raised against the all-or-none principle as applied to muscle.

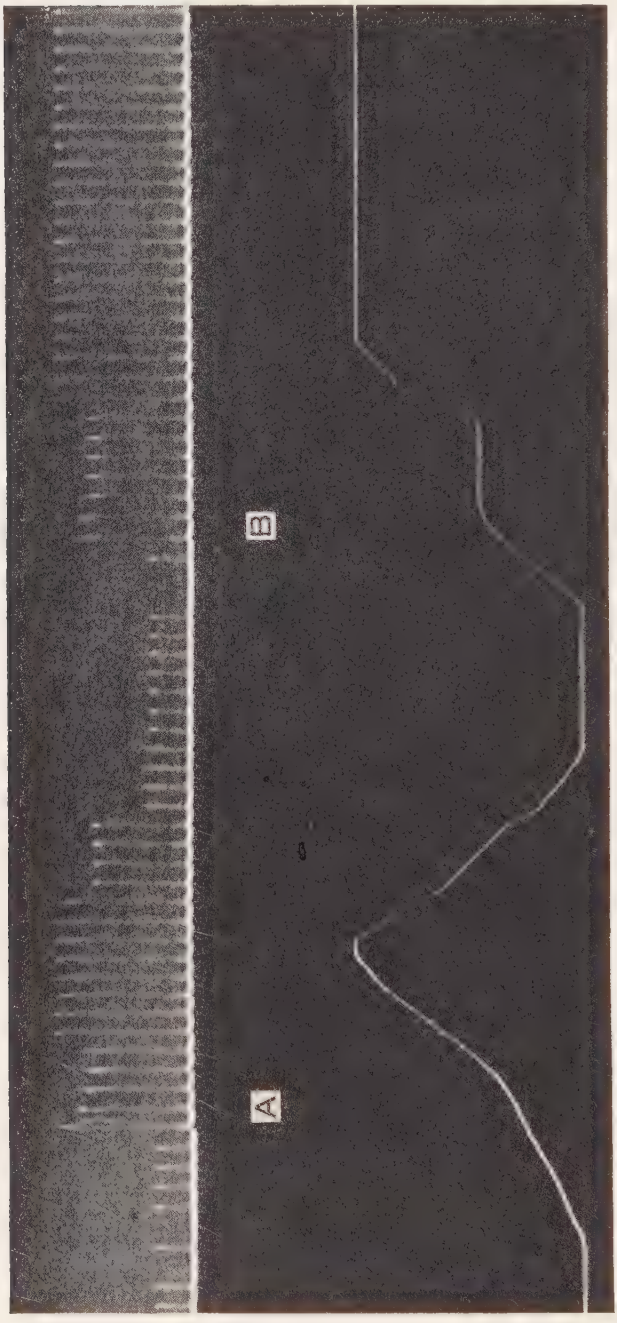

FIG. 13. The first portion of figure 12 enlarged

A CHRONOLOGICAL LIST OF IMPORTANT CONTRIBUTIONS TO THE PHYSIOLOGY OF MUSCLE

c. 375 B.C. ARISTOTLE. "De Motu Animalium." (Ed. princeps, *Aldus*, 1495–1498).

c. 180 A.D. GALEN, CLAUDIUS. "De Motu Musculorum. Libri duo." Nicolao Leoniceno interprete. *London: in ædibus Pinsonianis.* 1522.

1543 VESALIUS, ANDREAS. "De Humani Corporis Fabrica. Libri Septem," *Basil: Oporinus* [6 11.] + 663 + 17 pp., folio; 2nd Ed., *Oporinus*, [6 11.] + 824 pp., 1555, folio.

1618 FABRICIUS AB AQUAPENDENTE, J. "De motu locali animalium secundum totum." *Padua: J. B. de Martin*, 123+32+[8] pp. 4°.

1664 [CROONE, WILLIAM]. "De ratione motus musculorum." *London: I. Hayes apud S. Thomson*, [2] + 34 pp., 1 Tab., 4°.; 2nd Ed. *Amsterdam: C. Commelinum*, 34 pp., 1 Tab., 1667, 12°. (The first edition was anonymous; the second signed.) A later account was published in 1675 in Hooke's *Philosophical Collections*, No. 11, Sect. 8, p. 22, under the title: "An hypothesis of the structure of a muscle, and the reason of its contraction. Read in the Surgeons' Theatre, ann. 1674." This was subsequently translated into Latin and appeared in the *Acta Eruditorum*, 1682, p. 194, under the title: "De Motu Musculorum."

1667 STENO, NICOLAS. "Elementorum myologiae specimen, seu Musculi descriptio geometrica. Cui accederunt Canis carchariae dissectum caput, et dissectus piscis ex canum genere." *Florence: Ex typographia sub signo Stellae*, [4 11.] + 123 pp., 7 Tab., 4°; 2nd Ed. 1669, *Amsterdam: Janson*, 151 pp, 7 Tab., 8°.

1670 WILLIS, THOMAS. "Affectionum quae dicuntur et hypochondriacae pathologia spasmodica vindicata contra . . . . N. Highmorum. Cui accesserunt exercitationes medico-physicae duae: 1. De sanguinis accencione. 2. De motu animalium." *London:* 8°.; 2nd. Ed. *Leiden*, 1671, 12°.

1674 MAYOW, JOHN. "Tractatus quinque medico-physici, quorum primus agit de salnitro et spiritu nitro-aereo. Tractatus quatro: De Motu Musculari et spiritibus animalibus. Obiter de Motu cerebri: Nec non de Usu. Lienis & Pancreatis." *Oxford: Sheldonian Theatre*, [20 11.] + 335 + 152 pp., 6 Tab., 4°. (*portr.*).

1677 GLISSON, FRANCIS. "Tractatus de ventriculo et intestinis, Cui præmittitur alius, de partibus continentibus in genere; et in specie, de iis abdominis." *London: H. Brome*, [6] + 509 pp., 3 Tab., 4°.; 2nd Ed. *Amsterdam: Jacobus*, [30] + 591 pp., 1677, 12°.

1680 BORELLI, GIOVANNI ALFANSO. "De Motu Animalium." *Rome: Angeli Bernabò*, 2 vols., [12] + 386; [4] + 520 pp., 18 Tab., 4°. The 2nd Ed., *Lugd. Bat.* [*Leiden*]: *Peter v. d. Aa*, etc., [16] + 280 pp. + [16]; [4] + 264 + [16], 18 Tab., 1685, 4°.

1715 VAN LEEUWENHOECK, ANTHONY. "Observations on the fibres of the muscles." Phil. Trans. Roy. Soc., vol. 29, pp. 55–58.

1738 SWAMMERDAM, JAN. "Experimenta circa particularem musculorum in Rana motum, quae in genere ad omnes musculorum in hominibus aeque, ac brutis, motus adplicantur." pp. 835–860 of the "Biblia Naturae," 2 vols. *Amsterdam*, [32] + 910 + [18] pp., 53 plates

1751 WHYTT, ROBERT. "An essay on the vital and other involuntary motions of animals." *Edinburgh: Hamilton, Balfour, and Neill.* x + 392 pp.

1755 VON HALLER, ALBRECHT. "A dissertation on the sensible and irritable parts of animals." *London: J. Nourse*, xxxii + 79 pp., 8°. (Other editions in French, Latin and German appeared in this and the following year); see also "Musculi et motus animalius" in vol. 4, pp. 409–576 of Haller's "Elementa Physiologiae corporis humani," *Lausanne*, 1766.

1791 GALVANI, LUIGI. "De viribus electricitatis in motu musculari commentarius." Comment. Bonon. Scient. et Art. Instit., *Bologna*, vol. 7, pp. 363–418, 4 folding plates. 12 copies (Sylv. Thompson) were also published separately at Bologna "Ex typographia Instituti Scientiarum," in 1791; a 2nd ed., with additions of Aldinus and others, was pub. in 1792.

1797 VON HUMBOLDT, FRIEDRICH HEINRICH ALEXANDER. "Versuche über die gereizte Muskel- und Nervenfaser, nebst Vermuthungen über den chemischen Process des Lebens in der Thiere und Pflanzenwelt." *Posen* u. *Berlin: Decker*, 2 Bd.; [ii] + 495 pp., 8 pl.; 468 pp. French Trans. by J. F. N. Jadelot (1799) under the title, "Expériences sur le galvanisme, et en général sur l'irritation des fibres musculaires et nerveuses." *Paris: Didot*, 1 vol., xlvi + 530 pp., 8 pl.

1844 MATTEUCCI, CARLO. "Traité des phénomènes electro-physiologiques des animaux. Suivi d'études anatomiques sur le système nerveux et sur l'organe electrique de la tropille, par Paul Lavi." *Paris: Masson.* 348 pp., 4 pl.

1846 WEBER, E. H. "Muskelbewegung." Wagener's Handwörtebuch d. Physiol., Bd. 3, pp. 1–122.

1848 VON HELMHOLTZ, HERMANN. "Ueber die Warmeentwicklung bei der Muskelaction." Arch. f. Anat. Physiol. u. wissen. Med. (Müller), 1848, pp. 144–164.

1848 DU BOIS-REYMOND, EMIL. "Untersuchungen über Thierische Elektricität." *Berlin: Reimer*, 2 Bd., lvi + 743 + 608 + 384 pp.

1867 HERMANN, LUDIMAR. "Untersuchungen über den Stoffwechsel der Muskeln." *Berlin: Hirschwald.* 128 + 78 + 98 pp.

1871 BOWDITCH, HENRY PICKERING. "Ueber die Eigenthümlichkeiten der Reizbarkeit welche die Muskelfasern des Herzens zeigen." Ber. Sächs. d. Ges. d. Wissen., Bd. 23, pp. 625–689.

1882 FICK, ALBERT. "Mechanische Arbeit und Wärmeentwicklung bei der Muskelthatigkeit." *Leipzig: Brockhaus.* xiii + 287 pp.

1882 RICHET, CHARLES. "Physiologie des muscles et des nerfs." *Paris: Baillière.* viii + 924 pp.

1891 BLIX, MAGNUS. "Die Länge und die Spannung des Muskel." Skand. Arch. Physiol., Bd. 3, pp. 295–318; same title, *ibid.*, Bd. 5, pp. 150–206.

1891 SHARPEY-SCHAFER, EDWARD ALBERT. "On the minute structure of the muscle-columns or sarcostyles which form the wing-muscles of insects." Proc. Roy. Soc., vol. 49, pp. 280-286. [Independent contractility of the sarcostyles established.]

1902 GOTCH, FRANCIS. "The submaximal electrical response of nerve to a single stimulus." Journ. Physiol., vol. 28, pp. 395–416.

1907 FLETCHER, WALTER MORLEY, AND FREDERICK GOWLAND HOPKINS. "Lactic acid in amphibian muscle." Journ. Physiol., vol. 35, pp. 247–309.

1909 LUCAS, KEITH. "The 'All-or-None' contraction of amphibian skeletal muscle." Journ. Physiol., vol. 38, pp. 113–133.

1913 HILL, ARCHIBALD VIVIAN. "The heat production in prolonged contractions of an isolated frog's muscle." Journ. Physiol., vol. 47, pp. 305–324. [Recovery heat production described.]

1917 PRATT, FREDERICK H. "The all-or-none principle in graded response of skeletal muscle." Amer. Journ. Physiol., vol. 44, pp. 517–542.

1920 HILL, ARCHIBALD VIVIAN, AND WILLIAM HARTREE. "The four phases of heat-production of muscle." Journ. Physiol., vol. 54, pp. 84–128.

1921 MEYERHOF, OTTO. "Die Energieumwandlungen im Muskel. Milchsäurebildung und mechanische Arbeit." Pflüger's Arch., Bd. 191, pp. 128–183.

1921 SHERRINGTON, CHARLES SCOTT. "Break-shock reflexes and 'supramaximal' contraction-response of mammalian nerve-muscle to single shock stimuli." Proc. Roy. Soc., vol. 92B, pp. 245–258.

1923 FENN, WALLACE OTTO. "A quantitative comparison between the energy liberated and the work performed by the isolated sartorius muscle of the frog." Journ. Physiol., vol. 58, pp. 175–203.

CHAPTER I

The Broad Features of the Electrical Responses of Skeletal Muscle. Excitation. Chronaxie

As an aim of Part I of the present monograph is to elucidate the relation of the electrical response to other manifestations of activity in muscle, it will be desirable to review briefly for the reader the more general aspects of the problem of potential differences in irritable tissues. The historical development of our knowledge of electrophysiology has been described in the Introduction. The following account of electrical variations, I take to be the body of doctrine accepted by the majority of physiologists at the present time.

It is usually stated that the electrical response of muscle is caused by a transient increase in the permeability of a polarized interface existing somewhere within the substance of the muscle fibre (Lillie, *645*, and others; see Bayliss, *59*, Ch. XXII). The nature and morphological situation of this interface is not known, but the assumption of its existence, as we shall see, is well justified by a great variety of evidence, and we may therefore proceed directly to the interpretation of the electrical responses themselves.

RESTING MUSCLE

When two non-polarizable electrodes are placed directly in contact with two points on the longitudinal axis of an uninjured resting muscle, and led off to a sensitive galvanometer, no current passes through the instrument. In other words, all parts of such a muscle are in the same electrical state, *i.e.*, they are "isoelectric."

THE ACTION CURRENT OF MUSCLE

If galvanometer "leads" are taken from a functionally denervated (*e.g.*, curarized) strip of parallel-fibred muscle, or from a nerve similarly uninjured and at rest, and the proximal end of the tissue is then stimulated by an induction shock, a wave of electrical disturbance passes from the stimulated end to the distal end, and this gives rise to a characteristic deflection of the recording instrument. If such a deflection is recorded

photographically on a moving surface, the curve so described is *diphasic* in character. Electrical deflections produced in this way are due to "currents of action," or simply, "action currents." The two parts of the diphasic curve may for convenience be termed the first and second deflec-

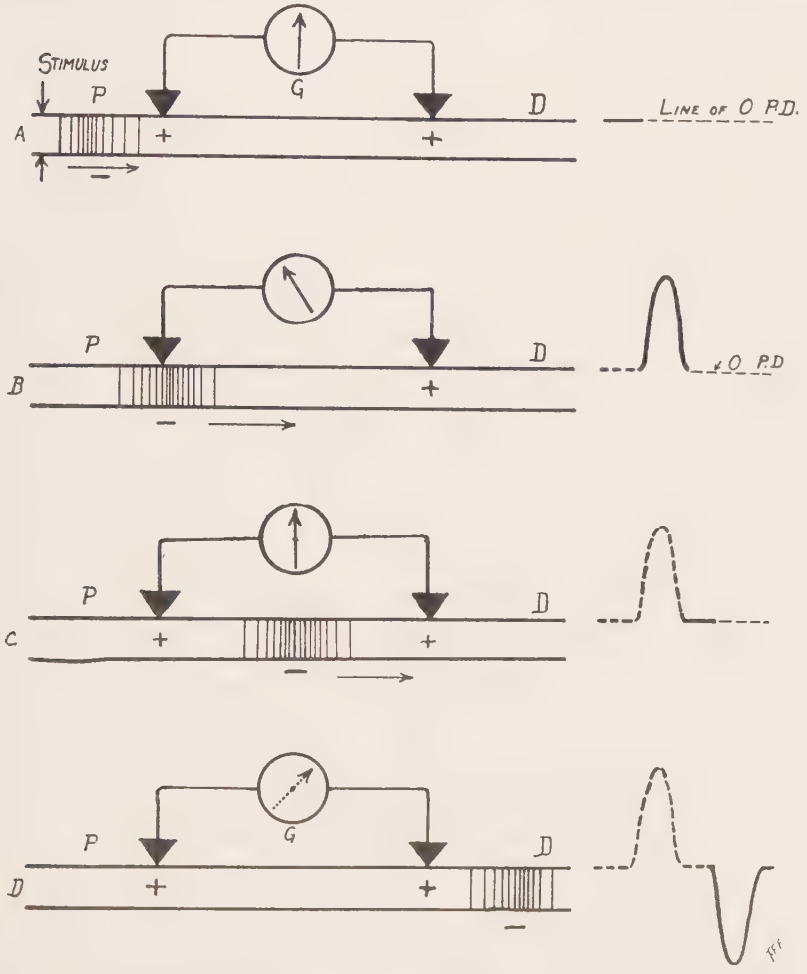

FIG. 14. Showing the conduction of the electrical disturbance along a strip of curarized parallel-fibred muscle (or along a nerve). The tissue is stimulated at *P*, the proximal end, and the resulting wave of electrical activity is represented at various stages in *a*, *b*, *c*, and *d*, as it progresses along the muscle to *D*, the distal end. On the right the resultant curves as described by the shadow of a galvanometer string are indicated.

tion. The first deflection is caused by the activity of the muscle strip beneath the stimulated or "proximal" leading-off electrode. This is shown diagrammatically in figure 14. The second deflection, which is in the opposite direction, results from activity under the distal electrode. This makes it evident that the electrical disturbance has passed from one end of the muscle to the other, and that the rate of travel of the disturbance may be deduced from the interval between the beginnings of the first and second deflections.

Now the first deflection is in the same direction as would be produced by connecting the proximal galvanometer "lead" to the zinc pole of a battery and the distal "lead" to a copper pole. The first deflection, as Waller used to say, is "zincative," *i.e., negative.* From this the general rule may be formulated that a region of a given tissue, when in a state of activity, is relatively negative to an inactive region of the tissue. It is customary in recording electrical responses to arrange that a negative deflection shall be recorded by movement in the upward direction, and in all the photographs in this work, unless otherwise stated, an upward deflection implies negativity *of the proximal contact.* The *second* deflection of a diphasic variation implies negativity of the distal contact, and, if preceded by an isoelectric interval (fig. 14*c*), this indicates that the proximal contact has come to rest. The stages in the progression of the wave of negativity along a strip of excitable tissue are shown in figure 14.

MONOPHASIC RESPONSES

Diphasic variations may be converted into monophasic variations by damaging (as by crushing) the excitable tissue immediately beneath one (usually the distal) leading-off electrode. This interrupts the physiological conduction of the wave of excitation, but does not interfere with the electrical conduction of the potential difference arising beneath the proximal contact. When the response of an irritable tissue which has been injured in this way is recorded, the curve consists of a single deflection in the upward direction.

Various methods have been employed in the past for obtaining monophasic responses: the portion of the muscle under the distal contact may be crushed, it may be scalded in boiling Ringer solution, or cauterized, or it may be rendered inactive by the application of a solution of some potassium salt, preferably K_2HPO_4 (Miss Buchanan's method). All methods have been employed with varying degrees of success, but they have all the disadvantages of destroying a portion of the tissue which is being investigated. In the case of sartorius muscle, Adrian (*6*) found that the burning of the distal end, necessary to render responses monophasic, usually caused the tension developed on stimulation to be

diminished more than half. The foreign proteins liberated as a result of burning a tissue appear to diffuse rapidly into adjacent uninjured areas and to impair activity, for (in keeping with Adrian) I have frequently noticed that a small burned area at one end of a sartorius muscle reduces tension development considerably more than if a corresponding length of muscle were excluded by tying a ligature. Consequently, monophasic electrical responses obtained by this method are to be looked upon with due caution.

When a muscle has a long tendon, a distal "lead" may be taken from the end of the tendon, which, being composed of inactive tissue, renders the responses largely monophasic without tissue destruction. Dr. Gasser has pointed out to me that on theoretical grounds a completely monophasic response is impossible unless all *surface* conduction (electrical) is eliminated (see *104*). Even in the case of a "monophasic" sartorius preparation the surface conduction appears not infrequently to cause a small second deflection. It has been found possible to eliminate this second deflection almost completely by using distally a silver chloride pin electrode, the sides of which have been insulated up to, but not including, a small area at the tip. This uninsulated point may be inserted into the tendon, or even into the bony parts to which the tendon is attached, and, owing to the insulation of the sides of the pin, the disturbance beneath the proximal lead remains uninfluenced by surface conduction. This method has been found preferable to those which involve tissue destruction, and preferable also to the K_2HPO_4-method, for it is difficult to limit the spread of the potassium solution and impossible to prevent surface conduction. The disadvantage of the insulated silver chloride electrode is the variability and large magnitude of its resistance. In nerve simple crushing of the distal end has been found the most satisfactory procedure for obtaining monophoric responses. (*226*, *227*, *287*, *288*, *386*, *387*.)

THE CURRENT OF INJURY OF MUSCLE (OR NERVE)

When a muscle is injured beneath the distal electrode, this portion of the muscle-mass becomes negative to an uninjured portion. Injury, in other words, leads to the same electrical condition as a state of activity. When led off to a galvanometer, a current, more or less constant, flows from the uninjured to the injured end. This current is spoken of as the "current of injury." If the current of injury were allowed to remain unneutralized and the muscle were to become active at the uninjured end, it is evident that the muscle would tend to become temporarily isoelectric again, and the galvanometer string would, for a brief interval, commence to return towards its zero point. An action current resulting from activity beneath a proximal electrode thus tends to neutralize an injury current emanating from beneath a distal leading-off electrode. That is, the injury current (as du Bois-Reymond expressed it) "undergoes a negative variation." This has led to the inference that the action current and the current of injury are due to the same cause, *i.e.*, a difference of potential between some structural interfaces within the fibre. This indeed is the necessary outcome of Brüning's important observation that if two sartorius muscles be damaged at their tibial ends and then placed

together in series, the E.M.F. of their injury current is approximately twice that given by one alone.

The belief that a simple concentration battery gives rise to potential differences comparable in origin to those occurring in living tissues is unjustified for the following reason (Brünings, *172;* Beutner, *98*, *99*, *100*). A concentration battery consists, as is well known, of two separate solutions of differing concentration connected by a salt bridge, but when connected in series by salt bridges, concentration batteries do *not* give rise to a summation of their respective potential differences. If connected by metallic electrodes, concentration potentials do summate owing to a selective effect of the metals for the anions in the respective solutions (Beutner), but this is in reality due to "polarization," and thus introduces a condition comparable to that existing in living tissues. Muscles, on the other hand, as Matteucci (*694*) early emphasized, *are* capable of summating their potentials when groups of them are connected so that their injured surfaces are in contact with the uninjured surface of the adjacent muscle. Drawing an analogy from the phenomena of voltaic electricity, Matteucci referred to his series of muscles as a *pile musculaire*. This indicates that injury potentials cannot be ascribed solely to the greater concentration of chemical bodies in the injured area (such, for example, as a greater number of H-ions) but must be attributed to pre-existing potential differences resulting from polarized interfaces. It is important to recognize this fundamental conception, otherwise one might look upon the injury current as due to a localized increase in H-ion concentration, and to this alone. If this were its sole cause, summation would not occur when successive strips of tissue are arranged in series. We have not of course excluded the possibility that the current injury may be considerably modified by this cause. However, the fact observed by Brünings (*172*) that the potential difference of two muscles connected in series is almost equal to the sum of the potentials of each one taken separately, suggests that the H-ion effect is relatively small (see Adrian, *13*, p. 309). This general conception of the causation of the injury current is strongly supported by the fact that the magnitude of the current of injury is found to be closely proportional to the absolute temperature (Bernstein, *91;* Adrian, *10*). Since the electrical energy is not derived from the damaged region, but rather from the regions of the tissue where the normal "membranes" are intact, one would anticipate that temperature alterations, if confined to the damaged area, would produce no effect on the size of the injury current, while if confined to the intact area, the change would be as great as if the temperature of the whole muscle had been altered. This has been found to hold true experimentally (*10*).

A simple method of visualizing the causation of the action current and the current of injury (in a nerve) is to construct a diagram such as that indicated in figure 15, which shows a cylinder with an inner central space and an outer wall. It may be imagined that the central space is filled with an aqueous liquid and that the outer wall is composed of an immiscible fatty substance. There will thus be an "interface" between the boundary of the water and the inner face of the fatty wall. If certain electrolytes are dissolved in the central aqueous phase a difference of potential will result between the water and the outside wall of the cylinder, provided the interface is not permeable to all of the ions contained in the aqueous

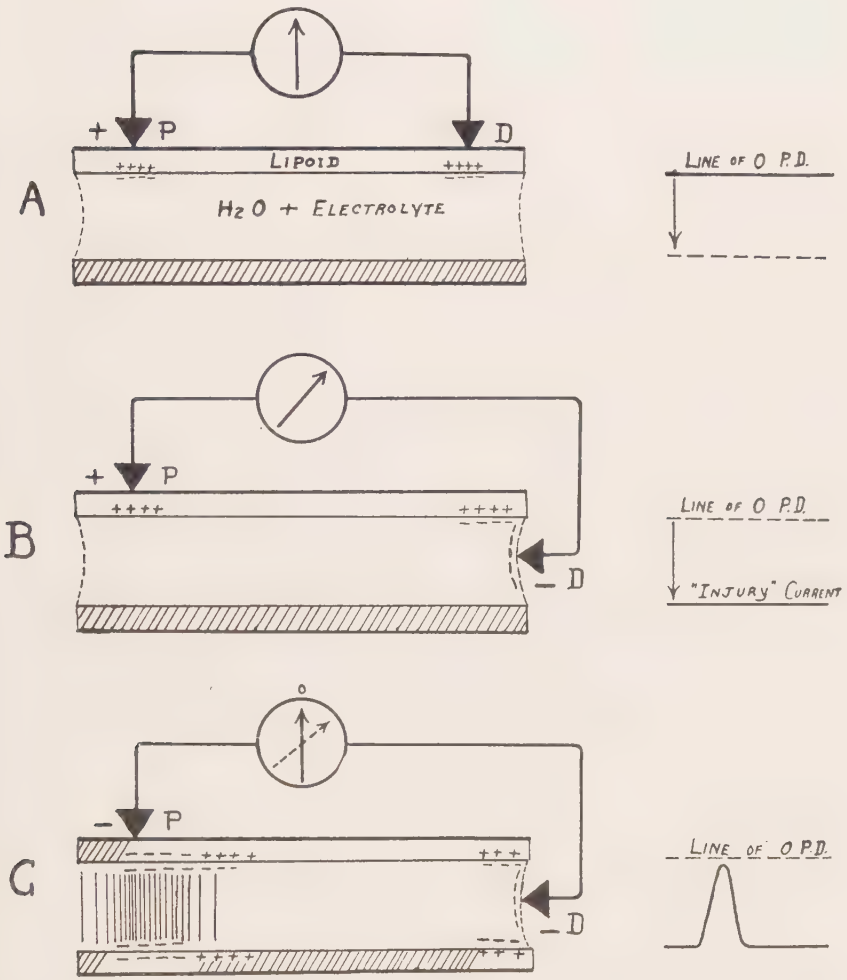

FIG. 15. A series of figures designed to show the nature of the current of injury and its relation to the action current.

A. The two leads, *P* and *D*, are taken from the "uninjured" outer surface of an oil-water cylinder (see text). No current passed through the galvanometer.

B. The distal lead, *D*, is now taken from the inside of the oil-water cylinder which is comparable to the injured end of a muscle or nerve. A current flows from *P* to *D* and this represents the current of injury

C. When the permeability beneath proximal contact, *P*, is transiently increased, the observed "injury" current undergoes a "negative variation," *i.e.*, the recording instrument tends to return to its base line as shown on the right of the figure. This variation is comparable to a monophasic action current.

phase. If now galvanometer "leads" are taken from two points along the outer surface of the cylinder no current will pass through the galvanometer (fig. 15*a*). If, however, one "lead," *P*, is taken from the inside (*i.e.*, the aqueous phase) of the cylinder and the other from the outer wall, a current will pass and we will assume that the inside is negative to the outside. If, instead of taking a "lead" directly from the inside of the cylinder, the permeability of the interface could be increased beneath one of the "leads," this "lead" would become negative as long as the enhanced permeability continued. If it were transient, the increase of permeability would cause a galvanometer deflection in every way comparable to a current of action; if, however, the increase of permeability remained constant (instead of being transient), this would cause a constant galvanometer deflection simulating in every way a current of injury. A current of injury, in other words, is equivalent to leading to the galvanometer from the inside and the outside of the polarized membrane of a tissue.

This example has been chosen because a nerve fibre is possibly constructed similarly to our oil-water cylinder. The medullated sheath of the nerve fibre is, however, probably not strictly comparable to the fatty wall of the cylinder, for the sheath is discontinuous, being absent at the nodes of Ranvier. In non-medullated fibres (Göthlin, *399*, *400*) and also in medullated fibres, as Klebs (*546*) early emphasized, there exists around the axis cylinder a thin layer of doubly refracting substance, probably fatty in nature, which forms an interface. It is possible, though the evidence is still far from complete, that this is the membrane chiefly concerned in conduction. The aqueous central portion of the oil-water cylinder in which electrolytes are dissolved is comparable to the axis cylinder of a nerve fibre. The so-called neurofibrils, along which conduction is by some (*95*, *110*) believed to pass, are held by Mott (*723*) to be artefacts, having no real existence in living nerve. Certain observers, notably Vernon (*723*), regard the evidence for the absence of neurofibrils as inadequate, since the ultramicroscopic method employed by Mott differentiates structures only so long as they have differing refractive indices. The fact remains, however, that no one has ever demonstrated neurofibrils in normal living nerve fibres, and Macdonald (*673*, p. 332) states that he has observed their formation within the axis cylinders of nerve fibres following injury, *i.e.*, during early stages of disintegration. It is therefore difficult to place confidence in theories of conduction which call upon the neurofibrils.

THE SHAPE OF THE RISING PHASE OF THE ACTION CURRENT

The shape of the electrical response of intact skeletal muscle has not been accurately determined; that is, it has not been recorded by an inertia-

less system such as the cathode ray oscillograph (fig. 16). In the case of surviving frog muscle, Lucas (*662*) and others have inferred the shape of the electrical variation from analysis of capillary electrometer curves, and there is no reason to doubt the general result obtained by such a method. These records were, however, taken from excised muscle, and in view of the rapid deterioration of frog muscle, when removed from the body (see Chapter III) into Ringer's solution, it is improbable that these curves represent accurately the course of the action current of intact muscle nourished by a normal circulation. The string galvanometer, for instance, shows that at constant temperature the electrical response is developed

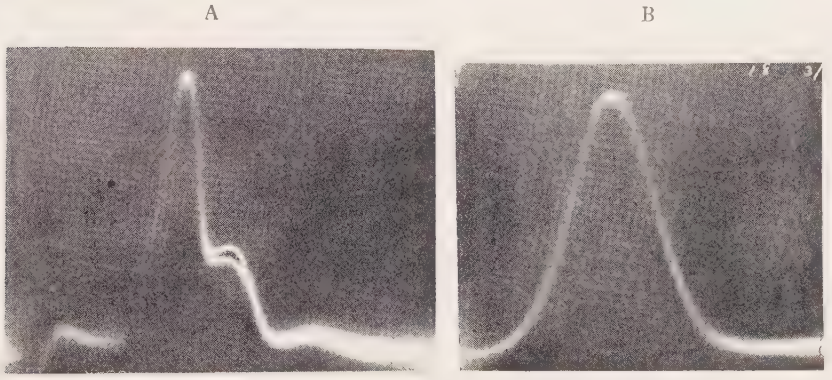

FIG. 16. A. A monophasic response of the sciatic nerve of bullfrog obtained with the inertialess recording system of Gasser, Erlanger, and Bishop (the cathode ray oscillograph) showing the α, β and γ waves on the descending limb of the curve. These are produced by groups of fibres of differing physiological characteristics.

B. A similar monophasic response of a "homogeneous" nerve, *i.e.*, one in which all of the fibres are of approximately the same physiological characteristics. Obtained through the kindness of Dr. H. S. Gasser.

more rapidly, the initial concavity, or "foot," is less pronounced and the whole response is briefer by several sigmata when the muscle is intact than when it is excised (*359*). The general shape is probably analogous in both excised and intact muscle, but when intact all the stages are somewhat more rapid than when excised.

In this connection, it is well to recall Lewis's observation on the heart (*629*, p. 70) that it "is an extremely sensitive structure, it is intolerant of injury and especially is it intolerant of nutritional change." The same is most certainly true of skeletal muscle, as we shall see in the following chapters, though the apparent dependence on the integrity of the circulation is less marked in lower (cold-blooded) animals than in mammals.

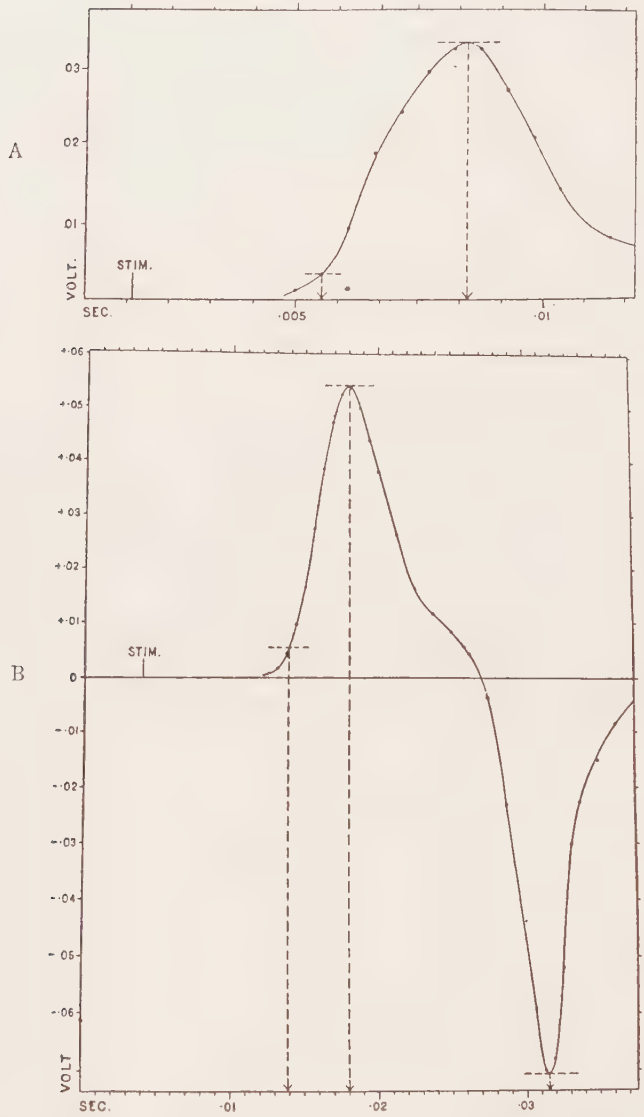

FIG. 17. Monophasic and diphasic action currents of curarized sartorius muscle (frog) plotted from an analysis of a capillary electrometer curve. Note the initial upward concavity in the rising phase. (Keith Lucas, *Journ. Physiol.*, vol. 39, p. 207.)

In figure 17 A and B, Lucas's monophasic and diphasic curves obtained from analysis of capillary electrometer records of a surviving frog sartorius

muscle are reproduced. It will be seen that the monophasic response is a *single* deflection reaching its maximum potential (at 18°) within approximately 2σ; after a brief crest it gradually subsides to the base line. The S-shaped ascent in this figure is noteworthy and its significance demands consideration. The point of inflection of this ascending curve (from concavity upward to convexity) occurs at a point more than 25 per cent above the total extent of the deflection. The point of inflection of the action current of an intact muscle, even when recorded by a galvanometer, is generally considerably lower, as we have just noted. Moreover, Erlanger and Gasser (*387*) found that this initial concave portion of the action current in the case of nerve becomes progressively less marked as the distance between the stimulating electrode and the proximal leading-off electrode is diminished, and this has been shown to be due in part to diminution in the degree of temporal dispersion caused by the slightly differing conduction rates of individual fibres. It is possible that part also of the gradual ascent is due to the travelling of the wave of increased permeability beneath the "leads" themselves. This raises the question of whether or not the initial concave portion of the action current is an artefact. Erlanger, Bishop and Gasser were unable in nerve to prove to their satisfaction that this initial gradual portion of the action current becomes completely abolished, even when recorded from beneath the stimulating electrode; they were, however, able to diminish it to a great extent. In string galvanometer records, there is always an initial period of concavity (even with instantaneous calibration currents; see figure 89) on account of the inertia of the string. Consequently the presence of this initial period is only of relative importance in string records, according as it is of greater extent than that which occurs when a rectangular current is passed through the string. One can reduce the height of the point of inflection of string records of muscle action currents by diminishing the area of leading-off electrodes (*359*), but it is never clear that the point of inflection is as low as that of a rectangular current. It follows from this that a small initial concavity is probably a normal physiological characteristic of the curve representing the rate of development of potential difference at a given spot of muscle or nerve, which is conducting a propagated disturbance.

The modified conception of the conduction of the nerve impulse introduced by Davis, Forbes, Brunswick and Hopkins (*227*) takes this feature of the electrical response into account. They point out that if, as is implied by the membrane theory of conduction, the local potential difference at one point serves to initiate a reaction at an adjacent point, "There must be a transfer either of energy or material, and such a transfer will occur only if there is a gradient of energy" between the two points. According to their hypothesis,

the action current, when at its height at any one point, would serve to alter the polarization of the semi-permeable interface (of the nerve) for some distance ahead of that point, on account of the necessary energy gradient. In other words, when the impulse sweeps down a nerve, the potential of the action current at a given point must begin its development gradually owing to the electric relations of the conducting mechanism. If the action current be recorded beneath a stimulating electrode, the initial concavity of the rising phase should, according to this conception, largely disappear. The experiments of Gasser and his coworkers (*104*) certainly indicate that the initial concavity becomes extremely slight (fig. 27) beneath the stimulating electrode, but the experimental evidence, as Dr. Gasser has pointed out to me privately, is difficult to evaluate, and one cannot as yet rule out the possibility that the diminution of the initial concavity with diminishing conducting distance is due entirely to diminished temporal dispersion (288).

CHARACTERISTICS OF THE STRING GALVANOMETER RECORD OF MUSCLE ACTION CURRENTS

The brevity of most physiological action currents, together with the inevitable inertia and resulting distortion of even the lightest string, have rendered it impossible to determine either the true shape of, or even the actual potential developed by the electrical responses of skeletal muscles of frogs and mammals (Gasser and Erlanger, *386*), but despite these inconveniences the string galvanometer yields information of great importance, especially if one adequately recognizes the limitations of the string record.

Parallel-fibred muscle. The shape of the string record differs considerably with the nature and disposition of the leading-off electrodes, with the method of stimulation, and with the particular muscle used.

a. Monophasic records of the responses of intact parallel-fibred muscle stimulated through its nerve (when the "leads" are taken proximally from the region of the incoming nerve and distally from the damaged tendon) are composed of a single upward deflection—provided due precautions are taken to prevent overshooting of the string. This is also true of excised muscle, but, as already mentioned, the magnitude of the deflection is somewhat less and the duration somewhat greater in surviving tissue.[1]

[1] A note which fell out of an old volume in the Radcliffe Library (Oxford) bears upon this question. It is in Burdon Sanderson's hand and seems worthy of record. "1. The properties of a sartorius which has been kept for 24 hours or more in 0.6 per cent of salt containing a trace of calcium salt are analogous to those it possesses in the fresh state (*i.e.*, immediately after excision). 2. The electromotive properties of such a muscle are less liable to change in consequence of evaporation (drying of the surface) and external injury. 3. It differs from a fresh muscle (*a*) in being less excitable by induction currents, (*b*) in its lower rate of conduction of the excitatory wave and of the wave of contraction, (*c*) in the duration and height (amplitude) of its isometric curve. 4. It can be curarized by the

It has been assumed in the past that in order to study the negative variation of muscle with accuracy an isolated, curarized, Ringer-soaked, parallel-fibred muscle, stimulated directly must be used. The aim of this drastic treatment was to exclude complicating factors such as nerve stimulation and injury currents. The differences between the electrical responses of a muscle stimulated indirectly and that of a directly stimulated curarized tissue were attributed to the exclusion of the nerve endings in the latter case, but the possibility that curare itself might be responsible for the differences (especially the greater duration of the action current in curarized muscle) have not, so far as I am aware, been considered. As we shall see in later chapters, the so-called "curare-effect" is in all probability due to a direct action upon the mechanism which produces the action current (*i.e.*, the polarized interface). Curare also prolongs the duration of the twitch and increases heat production by 25 per cent; in view of this it is unjustifiable to assume that curare acts solely

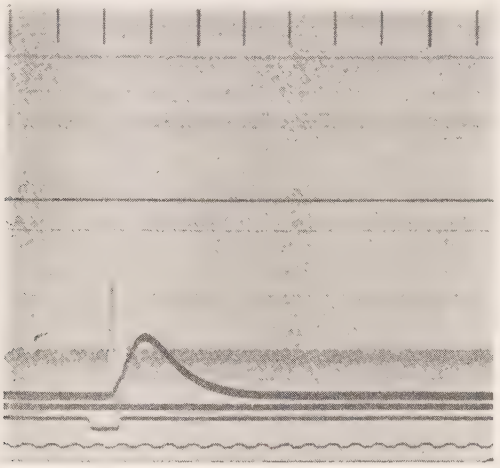

FIG. 18. A diphasic string galvanometer response of an intact parallel-fibred muscle (sartorius) of a frog at 18°; stimulated through its nerve. Mechanical response also shown.

on the "motor end-plate" (cf. Watts, *1031*). Consequently we cannot expect to study the physiological behaviour of electrical responses on curarized muscle. The action current of an intact muscle stimulated through its nerve must be the object of our study, whatever other inconvenience it involves.

b. Diphasic responses of a parallel-fibred muscle stimulated through its nerve are usually of small amplitude when both the "leads" are taken from *neural* portions of the muscle, for, owing to the rapidity of nerve conduc-

addition of curare to the solution in which it is contained and decurarized by transference to a solution not containing curare. 5. It can be similarly veratrinized and deveratrinized. 6. The effect on it of compression has not been investigated.

tion, groups of fibres may be excited almost simultaneously under both electrodes. If, however, one of the "leads" is taken from a *non-neural* portion of the muscle the amplitude of the excursion is considerably increased owing to the time interval between the commencement of the excitation between the two electrodes. The rising phase of a diphasic excursion is similar to, though briefer than, that of a monophasic, and the declining phase is more rapid, while the second part of the excursion (fig. 18) is similar to the first deflection but in the reverse direction. The duration of the second part of the excursion (below the line) is usually twice or three times greater than the first part of the excursion. If precautions are taken to prevent overshooting of the string, there is no evidence of further response at the end of the diphasic swing. The electromyogram of a parallel-fibred muscle is generally regarded as having the same shape as that of its constituent electrofibregrams (Lewis, *629*, p. 117), though temporal dispersion, owing to differing conduction rates, probably always slightly modifies the summated curve.

Diagonally-fibred muscle. The problem of interpretation and analysis of the action currents of a muscle in which the individual fibres are disposed diagonally (*e.g.*, pennate arrangement) and in which, therefore, the leading-off electrodes may lie on different fibres, have many points in common with the electrocardiogram. The electrical axis must be determined, the excitatory wave may "spread,"[2] all of the fibres may not be excited synchronously, and all of the constituent fibres may not have the same duration and size (*i.e.*, potential) of action current. Some fibres, for instance, in such a muscle are long and sometimes more or less parallel to the longitudinal axis of the muscle, while others are short and diagonally inserted into the tendon aponeurosis.

The *electrical axis* of a muscle has been defined as "the line along which the greatest electro-motive force is developed at a given instant of time, while the muscle is entering upon or recovering from the excitatory process. In a single fibre the electrical axis is in the same line as the fibre itself. In a *simple* strip of somatic muscle the electrical axis is necessarily set up or down the strip since all the fibres are arranged parallelly. In the heart (and in many skeletal muscles, *e.g.*, gastrocnemius) the fibres run at many different angles and the electrical axis is a resultant" (Lewis, *629*, p. 107) of the constituent electrofibregrams. As we shall see, the *spread* of the excitatory wave is so rapid in skeletal muscle stimulated through its nerve that the electrical axis does not change appreciably

[2] Along the individual fibres, of course, and not, as in the heart, from one fibre to the next, but since conduction rates in individual fibres vary slightly this implies some degree of asynchronism of the spread, as in the heart. This is a feature common to both parallel and diagonal-fibred muscle, but there are reasons for believing that it may be more pronounced in the latter.

unless extensive shortening occurs. In most diagonally-fibred muscles the electrical axis lies for simple mechanical reasons in the direction of pull, that is, longitudinally. When the fibres, in addition to being diagonal, are as in gastrocenemius also folded somewhat spirally (Beritoff, *84*; see below fig. 77), it is not necessarily clear that the electrical axis would be exactly along the longitudinal axis of pull, but as no determinations appear to have been made on this point it must be left unsettled.

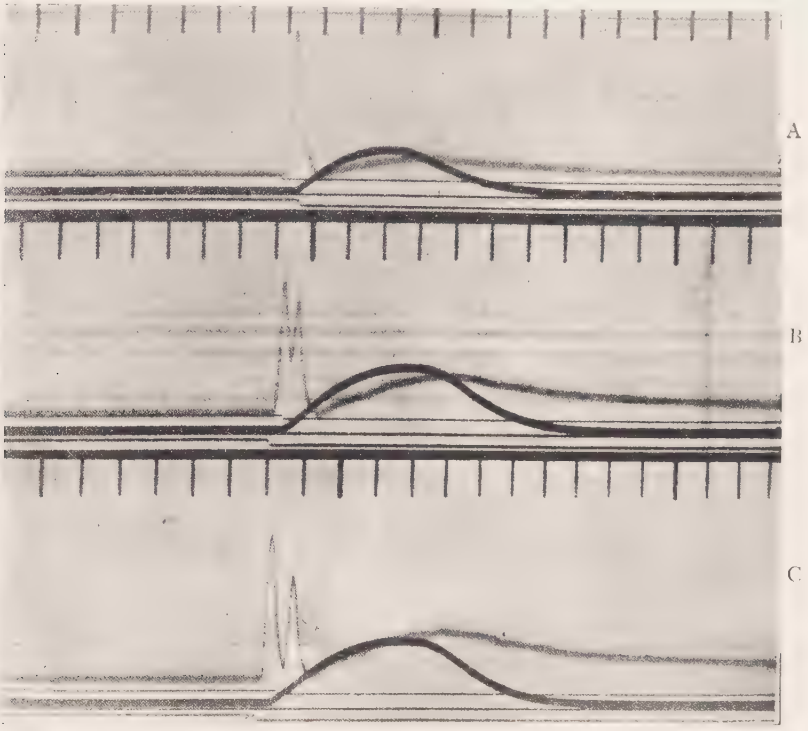

FIG. 19. Twitches of the intact gastrocnemius of a decerebrate frog in which monophasic electrical responses were obtained by placing K_2HPO_4 (1.3 per cent) on the distal lead. B and C are double responses separated by a brief interval. Moment of stimulation indicated by signals (both were break shocks). The second stimulus is not effective in A. Temperature 18°. The duration of the rising phase of the string in these responses lies between 4 and 4.5σ. Time above 0.02 second. Myograph frequency 1600 per second. Movement of string following action currents due to shifting of contact.

The size of individual action currents is not uniform in a diagonally-fibred muscle since the size of action current from individual fibres varies with the length of the muscle and inferentially, therefore, with the length of the constituent fibres (see Chapters VII and VIII). In a diagonally fibred muscle a given extension of the tendon causes unequal alteration in length of the constituent fibres (*361*); consequently, though many of the individual action currents may start at the same instant they will not necessarily cease

simultaneously. Moreover, in many muscles (*e.g.*, quadriceps extensor and gastrocnemius of cats) fibres of different physiological characteristics exist. There may, for instance, be an admixture of red and white fibres, and as Adrian (*12*) and others (*205*) have shown, the action current of a red fibred muscle is nearly four times as long as the duration of a white; consequently, the electrical responses of the red muscle will outlast the white, and in that way tend to slow the downstroke of the string record of white fibre action currents.

a. Monophasic string galvanometer records of the responses of diagonally-fibred muscles, *e.g.*, the gastrocnemius (cat or frog), are indistinguishable in general contour (see fig. 19) from a monophasic response of a parallel-fibred muscle. In general, however, they tend to be somewhat more pro-

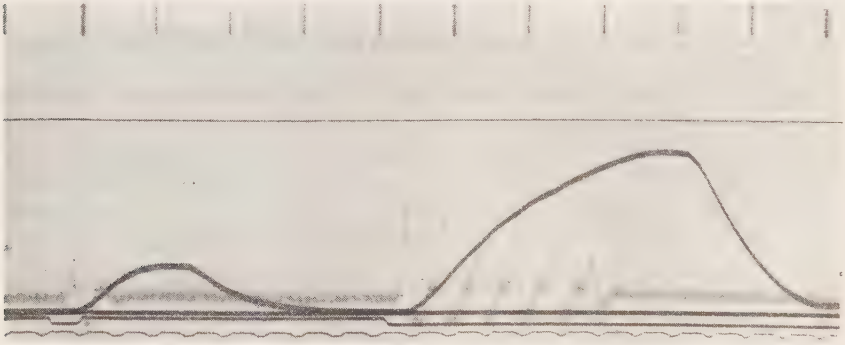

FIG. 20. A short tetanus of an intact gastrocnemius preparation at 50 per second showing the polyphasic character of the responses to individual stimuli. The last response is submaximal, which fact is reflected in the mechanical response by an initial concavity in the curve of relaxation (due to asynchronous cessation of contraction). This response was taken 5 min. after that obtained in figure 59A (Chapter V). Contrast in these two figures the sharpness of "angle." Time above = 0.04 second.

longed than currents obtained from parallel-fibred muscles under comparable conditions. Comparisons, however, are usually difficult on account of differing potentials of action currents from different muscles studied. Owing to the diagonal arrangement of fibres it is likely, however, that monophasic responses are not a faithful record of the course of the potential change in each individual fibre (Adrian, *13*).

b. Diphasic string galvanometer records of the responses of diagonally-fibred muscles. Since a small second excursion below the line is extremely difficult to avoid when one attempts to record monophasic responses, the characteristics of diphasic responses of diagonally-fibred muscles demand consideration. Such diphasic responses differ from other responses so far considered in that they are usually polyphasic, that is, there often occur

(after an interval of from 6 to 18σ) secondary *negative* responses after the main first response has passed away (fig. 20, and see figs. 35 and 38, Chapter III). The secondary responses, however, are always very small, never being more than one-twentieth of the amplitude of the first response. Polyphasic responses to single stimuli have been observed in the present investigation in the gastrocnemius of frog and cat, and in quadriceps of the cat.

This type of response has also been obtained, and the effect on it of temperature investigated by Judin (*530, 532*). He finds that while the period of the first deflection is influenced by temperature, the periods of the succeeding small deflections are not so influenced, and Judin infers from this that small deflections are therefore attributable to physical causes. Polyphasic string records have also been noted by many others in the diphasic responses of gastrocnemius (see Jolly, *525*, pp. 223–224). Buchanan (*177*, p. 8), for instance, found a second deflection in the response of gastrocnemius to nerve stimulation of 6σ after the first. She believed that it was due in some way to the arrangement of fibres in gastrocnemius for she never found them in sartorius. Jolly maintains that the existence of these secondary responses proves that the response of a muscle to a single stimulus is "usually oscillatory in character."

The fact that the secondary electrical deviations are present *only* in the diphasic response of a diagonally-fibred muscle is strong presumptive evidence against Jolly's view that the normal responses to a single stimulus are oscillatory in character, and also against Judin's belief that these secondary oscillations are caused "physically" (*e.g.*, by the beginning of shortening).[3] They are never in my experience found in the diphasic response of sartorius. They would appear, therefore, to be associated in some way with the presence of diagonal fibres and asynchronous cessation of individual action currents among the fibre groups suggests itself as a possible cause. Some fibres in gastrocnemius are short and others are long. As each fibre probably receives but one motor end-plate (Chapter VI) the duration of activity will vary with the length of the fibre.

It will be recalled that a condition very similar to this occurs in the heart. Following the initial stage of *invasion, i.e.*, the period of spread of the excitatory wave, in Lewis' terminology, there is a *stage of possession* during which the whole muscle between and beneath the two electrodes is in a state of isopotentiality owing to all the fibres being uniformly involved in the excitatory process. There is then the *stage of retreat* or period of recovery, during which the excitatory process is passing away beneath the distal electrode (causing the second portion of the diphasic excursion).

[3] I cannot agree with Judin that the period of the second deflections are completely uninfluenced by temperature.

But owing to the fact that the stage of retreat is not simultaneous in all the fibres, the electrical manifestation of its termination, *i.e.*, the *T* wave of the electrocardiogram, tends to be irregular in amplitude, shape and even in direction, being sometimes positive and more often negative. Local cooling, for instance, in the case of the heart has been shown to reverse the direction of this final (*T*) wave (Lewis, *629*, pp. 116–122). There are thus many reasons for believing that the *T* wave of the electrocardiogram results from a condition similar to that underlying the causation of the secondary deflections in diphasic responses of diagonally-fibred muscles. It is clear, for instance, that when the two galvanometer "leads" from a muscle do not lie on the same fibres the stage of retreat may have passed away under both pairs of electrodes while the non-neural portions of the muscle or any fibre groups which for other reasons act more slowly (*proximal* to the proximal electrode; or distal to the distal) are yet in the stage of invasion or possession, and in this way they may influence indirectly either one or other of the two electrodes. It is more likely in the case of gastrocnemius that the proximal electrode, since it is surrounded by fibres, would be the one so influenced (as the distal "lead" is on the inactive tendon). This is much the same explanation which Lewis has given for the occurrence of the *T* wave in the electrocardiogram.

It may be urged that the greater interval between the main wave and the *T* wave of the electrocardiogram (230σ) as compared with that between the corresponding waves of the electromyogram of gastrocnemius (6 to 18σ) is against the inference that they are similarly caused, but Lewis has pointed out that the interval between the *S* and *T* waves in the heart corresponds closely to the total duration of the monophasic response (Lewis, *629*, p. 59, fig. 36), and it is clear that 6 to 18σ correspond roughly with the duration of monophasic responses (10σ) of gastrocnemius (see fig. 20). Another, though perhaps less likely explanation, of the polyphasic character of these responses is that they are produced by the superposition of two phasic action currents of different characteristics (duration, latency, etc.) resulting from muscle fibre groups of different physiological characteristics such as "red" and "white" fibres, or Grützner's (*425*) "quick" fibres (poor in sarcoplasm) and those rich in sarcoplasm (cf. Bonhöffer, *126*). It is not known that an admixture of red and white fibres exist in gastrocnemius (frog), and Grützner's classification of fibres on the basis of sarcoplasmic content was made among the fibres of sartorius whose action current is not polyphasic.

The explanation just given of the origin of polyphasic responses has recently been strongly supported by Adrian's (*13*) careful analysis of the responses of the tenuissimus muscle (cat).[4] When the tenuissimus is

[4] The nerve supplying this long slender muscle divides, as shown in figure 1 of Adrian's paper, just before entering the muscle. When stimulated directly the contraction spreads throughout the entire muscle. When stimulated, however, after the nerve is cut below

curarized and stimulated directly the contraction spreads only about 15 mm. in either direction from the spot stimulated, *i.e.*, in all only about 30 mm. contract. In keeping with this Adrian has found that the average length of muscle fibre in tenuissimus is about 20 mm. so the failure of a contraction wave to conduct itself further clearly results from the length of the fibre and not from conduction with a decrement. He finds that an electrical response is only to be obtained when one "lead" is on the region which contracts, and the response is only truly monophasic when the

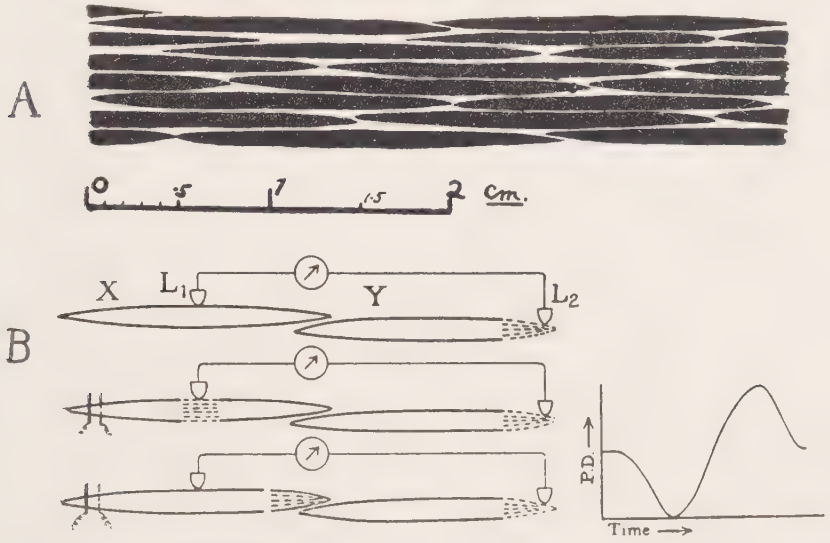

FIG. 21. A. The arrangement of fibres in tenuissimus of the cat as demonstrated by Adrian.

B. The electrical consequences of this arrangement when the galvanometer leads are taken from two adjacent fibres. Fibre Y is injured and X only is stimulated. A diphasic response results; had X and Y been two parts of the same fibre the response would have been monophasic (*Journ. Physiol.*, vol. 60, p. 308).

distance between the "leads" is reduced to 10 mm. or less (the distal "lead" being on an injured spot of muscle). This is illustrated in figure 21, which

its bifurcation only that portion of the muscle responds which is supplied by one division of the nerve. If now the nerve is severed above its division stimulation of one-half causes contraction of the whole muscle. This suggests that a large proportion of individual fibres bifurcate, and such in fact was found to be the case when the number of fibres in the main trunk were counted and compared with the sum of the fibres in each of the two branches. This shows clearly that one nerve fibre may supply more than one muscle fibre and in different parts of the muscle (see p. 369).

is taken from Adrian's paper. With nerve stimulation (or, which amounts to the same thing, the direct stimulation of an uncurarized muscle) the galvanometer responses are always polyphasic and become apparently increasingly so as the distance between the "leads" is increased. Adrian (*13*) has also found polyphasic responses in the cat soleus and gastrocnemius. He attributes polyphasic character of the (single) responses to the arrangement of the fibres and the resulting slight asynchronism of the response.

VARIATIONS OF THE DIPHASIC GALVANOMETER RESPONSE WITH THE POSITION OF THE ELECTRODES

This has been investigated incidentally by many authors. Recently Samojloff (*840*) has found that three characteristic curves may be obtained from gastrocnemius when the proximal electrode is placed in three successive positions, the distal remaining fixed (on the tendon): (1) When the proximal "lead" is taken from the *sciatic* nerve just as it enters the muscle the action current of the nerve may be seen in the record at a brief interval before that of the muscle (fig. 22A). The interval between the two action currents provides a rough index of the time lost at the motor end-plate. The muscle action current under these circumstances has the same characteristics as (2), when the proximal "lead" is taken from the *origin of the muscle* in the region of, but not on, the incoming nerve. In this case the initial deflection of the muscle action current is downward (fig. 22B) resembling the *Q* wave of the electrocardiogram, but it is followed by a large negative deflection (the *R* wave), and finally by the usual second deflection of the diphasic excursion, the *S* wave. Since these deflections are caused similarly to those of the electrocardiogram there is no reason why they should not be similarly designated. The *Q* wave of Samojloff's muscle action currents results from the fact that the distal electrode is affected by the negativity of the fibres excited in the belly of the muscle, before the proximal electrode is affected by that negativity. When, however, (3) the proximal electrode is moved to the middle of the muscle (fig. 22C) the *Q* wave disappears and the simple diphasic *R-S* complex remains. It is this latter type of response which has always been obtained in the course of the experiments recorded in this monograph. An attempt has usually been made, however, to render the responses as nearly as possible monophasic without tissue destruction.

The effect on the *size* of the electrical response of the distance between the leading-off electrodes has been investigated incidentally in the course of the present work, and it has been found that provided the electrodes are

15 to 20 mm. apart the size of the electrical response is at its maximum, and this maximum remains practically constant as the "leads" are further

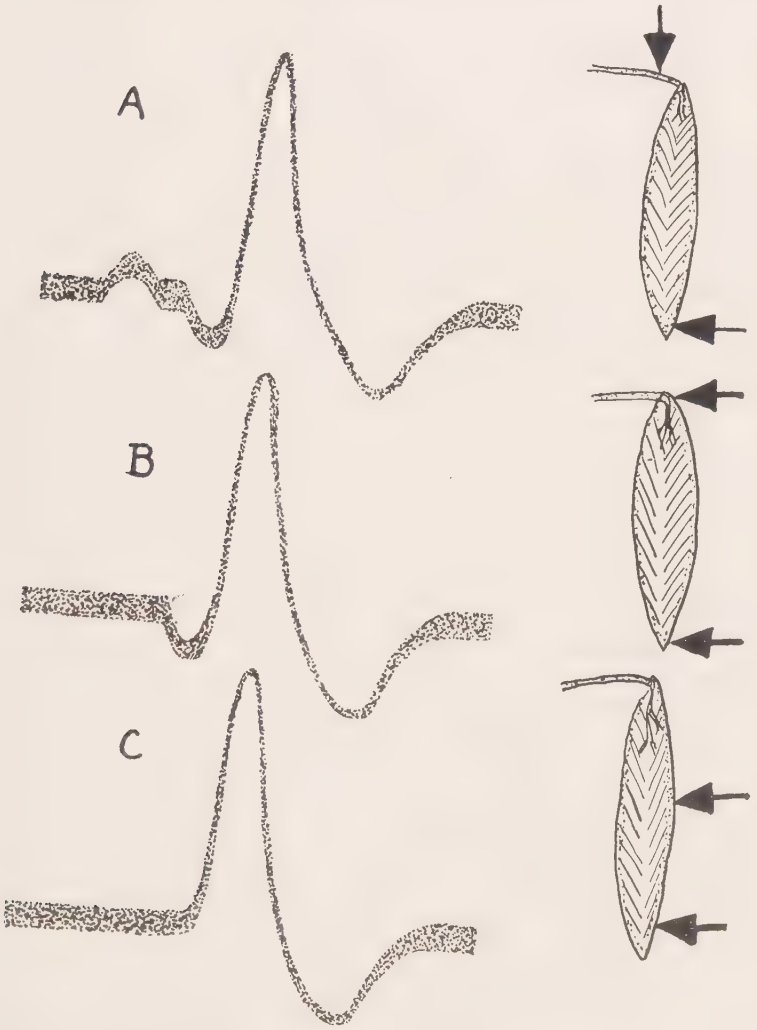

FIG. 22. Variations in the action current complex with variations in position of the leading-off electrodes (after Samojloff, *Pflüger's Arch.*, Bd. 208, p. 508).

separated. When placed more closely together than 15 mm. the electrical responses diminish. Thus, when 5 mm. apart the electrical response may be only one-third of its maximum size.

Adrian (*13*) has pointed out that in the case of muscles with diagonally arranged fibres increase of the distance between the "leads" increases the tendency of the responses to single stimuli to become polyphasic. The augmentation of electrode area has a similar effect.

THE MEMBRANE THEORY OF EXCITATION AND THE ELECTRICAL CHANGE

A detailed account of the theory of the origin of the electrical change would be out of place here, especially in view of the recent admirable treatment of the subject by Davis (*224*) and Lillie (*645*; see also *100–101*, *59*, Chs. XIII and XXII). The general principles, however, may be stated as follows. Within living cells interfaces occur between such unlike phases, for instance, as oil and water. Phase boundaries of this nature are referred to, rather inaccurately, as membranes. It is usually stated that when such a membrane is permeable to all the ions dissolved in either of the phases there can be no electromotive force present if equilibrium is established (i.e., provided there are no "concentration" potentials). When, however, such a membrane is permeable to some ions and not to others, a difference of potential must exist between the two sides of the membrane owing to the resulting Helmholtz double layer, and such a membrane is said to be polarized (cf. *605*). Now electrical potentials are set up in excitable tissues when local alterations occur in the permeability of the membrane. In muscle (and nerve) the polarization is such that *anions*— to which the membrane appears to be impermeable when in the resting state—lie *within* the membrane, and the layer of *cations* is held by attraction on the outside. This is shown in figure 15. If stimulated these surface conditions become altered, and when induction shocks are used as stimuli—the cations being attracted toward the cathode of the stimulating electrode, and the anions being repelled—the electrical double layer is altered with the result that the permeability of the membrane increases. This altered permeability lasts longer than the stimulus which produced it, and the portion of the muscle in which the surface properties are thus modified becomes, as we have seen, electronegative to the unstimulated parts of the fibre.

According to the membrane theory, the action current set up locally serves to depolarize adjacent portions of the membrane and in this way the process propagates itself as a wave from one end of the fibre to the other. If this view—which has found ample support in the experiments performed by Lillie (*644*), Davis and coworkers (*227*) and others—is accepted, the action current at one point serves as an adequate stimulus for adjacent points (*v. supra*). As Lewis (*629*) has remarked (p. 59), "the

muscle strip may be regarded as composed of a number of minute batteries, discharging while connected up in parallel. The effects, as they are displayed, are witnessed in the muscle strip treated as a whole; but they represent the events in each of the individual fibres of the strip, and it is correct so to visualize them." Such, in very brief outline are the general principles of the membrane theory.

Mathematical treatment of the problem of excitation has been given by several authors, notably Nernst (*731*), Hill (*470*), and Lapicque (*595, 601*), and while the results are suggestive and even promising, doubt has arisen concerning the initial assumptions (membrane dimensions, diffusion constants, etc.) necessary for mathematical formulation. It is also questionable whether the experimental data used in previous mathematical treatment were sufficiently accurate to yield significant results (*223, 224*). The resistance and capacity of the tissues on which strength-duration values have been made have not been given adequate consideration, and recent investigations (*521, 522, 605*) make it evident that variations in these conditions are of sufficient consequence to vitiate many inferences drawn from previous work. The varied nature and size of the stimulating electrode have also introduced errors of importance (*11, 223*; see also *103a, 104*). For the present, therefore, satisfactory mathematical analysis is not feasible.

There are certain additional points which the assumption of a polarized interface within the tissue cells makes it necessary to consider.

The *sine quâ non* of polarization is molecular arrangement, and we may consider what evidence exists for an orderly disposition of the atoms and molecules in tissue cells. Klebs (*540*) and others (*399*) have observed in the case of nerve that the individual fibres are doubly refracting, and this indicates that molecules within the nerve must be arranged in orderly sequence. From the work of Donnan, Bragg and others it is evident that the most likely place for the occurrence of an orderly sequence of molecules is at an interface. Since Göthlin (*400*) has found that the double refraction occurs both in the medullary sheath and the axis cylinder it is evident that somewhere in both of these structures, layers of regularly arranged molecules are to be found, and it is therefore probable that the region common to both these phases would be the seat of this regular molecular distribution (see above, p. 62). Moreover, Klebs in his original investigations (1865), noted that the area of double refraction corresponded to the region axis cylinder-sheath interface. Turning to muscle, the well-known doubly refracting character of individual fibres similarly provides evidence of molecular arrangement at interfaces within the fibre (Garner, *378*). For a detailed account of the optical conditions of muscle, one may consult the exhaustive thesis of F. Vlès(*1003*). We have no direct evidence, however, as to where morphologically the interface responsible for the action cur-

rent is situated (Chapter IX). We shall see that Tiegs (*981*) identifies this polarized surface with the so-called helicoid membrane which he believes to characterize the structure of all striated muscle fibres.

THE RELATION BETWEEN THE PROPAGATION OF THE ELECTRICAL RESPONSE AND THE MECHANICAL RESPONSE

We owe to Bernstein (*88*) the first satisfactory demonstration that the electrical response and the mechanical response travel along the muscle fibre at the same rate. In the curarized sartorius muscle he found that the rate at which the electrical disturbance passed down the fibre is exactly the same as the rate at which the wave of contraction (as recorded by thickening) travelled. He believed moreover that the contraction wave always followed slightly in the wake of the electrical disturbance. Recent observations show that the interval between the beginnings of the two waves is not more than 1.5σ (Chapter II). It thus is clear from their propagation rates that the electrical and the mechanical responses are *not* independent and separable processes but are intimately related one to the other. The fact that the rate of conduction of electrical and mechanical responses have the same temperature coefficients further substantiates this conclusion.

CHRONAXIE[5]

In studying different irritable tissues it is important to have some basis for comparison of their excitable properties; also it is equally desirable to be able to contrast the properties of the same tissue in different physiological (or pathological) states. In a rough qualitative way this may be estimated by determining with a potentiometer the minimal voltage (of a constant current) necessary for stimulation, *i.e.*, the determination of the galvanic threshold. The threshold may also be found for faradic currents. But it is sometimes observed that relatively sluggish tissues will respond to constant currents of smaller intensity than serve for excitation of a rapidly responding tissue. On the other hand, sluggish muscles often fail to respond to a faradic stimulus whatever its intensity may be. It has been found that irritable tissues are to be distinguished from each other not by their threshold of excitation, but by the *duration* of the exciting stimulus (galvanic). In general the sluggish tissues require a stimulus of long duration, while a "rapid" tissue (which may have the same threshold for galvanic currents) is stimulable by briefer currents.

[5] An interesting history of the development of chronaxial conceptions has recently been written by Lapicque (*604*).

For routine comparison it is essential to use a strength of current somewhat above the threshold in order to guard against adventitious alterations in tissue resistance (due to moisture, etc.). It is usual to employ a current of double the threshold intensity, and the minimal effective duration of such a current is referred to as the "chronaxie" (Lapicque) or "excitation time" (Lucas). In Lapicque's (*598*) words chronaxie has been defined as "La durée du passage du courant constant à début brusque qui atteint le seuil de l'excitation avec une intensité égale au double de le rhéobase, soit pratiqué avec le voltage double du voltage rhéobasique." The *voltage rhéobasique* refers to the intensity of the threshold stimulus, *i.e.*, the intensity in volts of a constant current closed instantaneously which will just excite if continued indefinitely (see *350*). The apparatus necessary for chronaxie determination is described in the appendix.

It has been found that every irritable tissue has a characteristic chronaxie. In the case of the gastrocnemius muscle of the frog the chronaxie is notably short, *viz.*, 0.3 to 0.5σ. In general the more rapidly moving muscles have the briefer chronaxie, and various other physiological characteristics of irritable tissues have been found to vary according to their chronaxie. Thus the briefer the chronaxie of a given tissue: (*a*) the more rapid the rate of conduction of the wave of excitation; (*b*) the more rapid the rate of development of the action current, (*c*) the briefer the summation-interval for subminimal-stimuli (*16*); (*d*) the briefer the refractory period; in muscle (*e*) the shorter the latent period, and (*f*) the shorter the duration of the isometric twitch (*152*). Further details concerning these relationships will be found in Chapter XIII of Lillie's (*645*) book. A consideration of these relationships has led Lewis (*629*) to the enunciation of what he has termed the "Law of cardiac muscle" which he has defined as follows: "The fundamental properties of muscle under physiological conditions will be found to vary quantitatively in the four types of cardiac fibre, if, for any two types, we can obtain a measure, then within reasonable limits we may predict the quantity for the remaining two types by placing all four in their natural order." This is illustrated in the following table given by Lewis (*629*, p. 97):

TABLE 1.

FIBRE	FIBRE SIZE	RATE OF CONDUCTION	DURATION OF SYSTOLE	REFRACTORY PERIOD
Nodal	1	1	[4]*	4
Ventricular	2	2	3	3
Auricular	3	3	2	2
Purkinje	4	4	[1]	1

* Figures in brackets as yet theoretical.

As an example of the application of this law, one may take the fact that the duration of ventricular systole is greater than that of auricular systole. By application of the law one may infer from this that the rate of conduction is more rapid and the refractory period less in the auricle than in the ventricle. Applying this same law outside of the field of cardiac muscle one may infer with equal safety—when, as in the case of mammalian nerve, the rate of conduction is higher than in frog nerve—that the refractory period and the duration of the rise of the electrical response will be briefer in mammalian nerves than in the frog.

An observation of Erlanger and Gasser (*287*, *104*) which may appear to be contrary to this law is that, though the action current of the α fibres travels more rapidly than the action current of the β fibres of the sciatic nerve of the bull-frog, yet the rate of rise to maximum of these action currents—as determined by the cathode ray oscillograph—is very nearly identical for the two. In a few cases, however, the rate of rise of the β wave was somewhat slower than in the case of the α wave, which would be in accord with the implications of Lillie's theory. It may be pointed out, however, that even if the difference between the rate of rise in the two curves is not always obvious this is not necessarily a serious objection against Lillie's view, since here we are dealing with relatively slight differences in conduction rate. The rate of conduction of the α wave is about 40 m. per second and that of the β wave 25 m. per second. The correlations on which the theory was based were made on gross differences of conduction rate. In addition to the rate of rise of the potential there are other factors which influence the velocity of conduction; namely, the threshold of stimulation and the electrical resistances of the fibres (*224*). Now the threshold of the β fibres is considerably higher than that of the α fibres, and this in itself would lead one to anticipate slower conduction. In the case of the α and β waves various complicating factors, such as the area of the leading-off electrodes and the tendency of the individual waves to spread out owing to slight differences in the conduction rates of individual fibres, may easily tend to mask any slight differences which may exist in the rate of ascent of the action currents of individual fibres. Another point in favour of the Lillie theory of conduction, disclosed by the cathode ray oscillograph, is the fact that when travelling in the relative refractory period in which conduction is considerably slower than in the fully recovered nerve fibres the duration of the rising stage of both the α and β waves is increased (*387*).

The investigations on the chronaxie of excitable tissues have led to an important generalization concerning the mechanism of the curare effect. The Lapicques (*597*, *603*, *607*, *608*) have found that unpoisoned muscle fibres tend to have the same chronaxie as their motor nerves. Since, however, the chronaxie of a muscle is determined by insertion of silver chloride pin electrodes directly into the muscle substance it may be urged very justly that it is the chronaxie, not of the muscle fibres themselves, but of the intramuscular nerves which is determined. Indeed, Lapicque's views have received criticism on these grounds, but criticism based upon this alone comes from a failure to examine his evidence fully. It is ad-

mitted that the intramuscular nerves are stimulated in this way; however, after curare has just caused a block for stimulation by the nerve, the chronaxie of the muscle is found to be double that of the nerve (but Cf. Watts, *1031*), and if the curare continues to act the chronaxie of the muscle continues to increase (*597*, *607*). If, on the other hand, the curare-effect is brought about by strong strychnine (1 in 1 to 2000) applied peripherally, the chronaxie of the nerve trunk, when the block is just effective, is found to have sunk 0.15σ, or less, while that of the muscle remains "normal," *i.e.*, at 0.3σ or thereabouts, which is the chronaxie previously possessed by the nerve (*608; 432*). From this the conclusion is drawn that normally there exists a condition of iso-chronism between a motor nerve and a voluntary muscle which it innervates, and that curarization is brought about when the time relations are disrupted to such an extent that the chronaxie of one differs from the other by a hundred per cent, in other words, heterochronism results in curarization. In favour of the theory of iso-chronism it may be noted that Jinnaka and Azuma (*521*) obtained a value of 0.3σ for the chronaxie of the non-neural portion (sartorius) of a single muscle fibre using a pore electrode. Davis has obtained the same result (unpublished). It is only fair to say, however, that there are certain inherent difficulties in the theory of iso-chronism (*1004*, *1031*), and while as a generalization it is possibly adequate, it is not yet justifiable to place unreserved confidence in the theory as it stands. There can be no doubt but that time factors are important in determining an optimal stimulus, and conditions which upset normal time relations tend to make stimulation of one tissue by another difficult or impossible. But it is not proved, and indeed it is improbable that duration, *per se*, is the only factor. Other circumstances, such as the rate of development and size of the potential, and the shape of curve along which it develops, are also to be considered. The theory of iso-chronism appears to be too mechanical in its literal interpretation, and it seems more proper to regard it as an expression of a tendency rather than as an unalterable condition of stimulation. (See Vogel, *1004*.)

Theoretically there are four possible ways in which curarization might be brought about (*608*):

		Chronaxie
1. Curare	Muscle	Augmented
	Nerve	Unaffected
2. Strychnine	Muscle	Unaffected
	Nerve	Diminished

3. Strong veratrin, nicotine or physostigmine.....	Muscle	Diminished
	Nerve	Unaffected
4. (?).....	Muscle	Unaffected
	Nerve	Augmented

It will be seen that only three methods of producing curarization are realized practically, as there is no way as yet known for increasing the

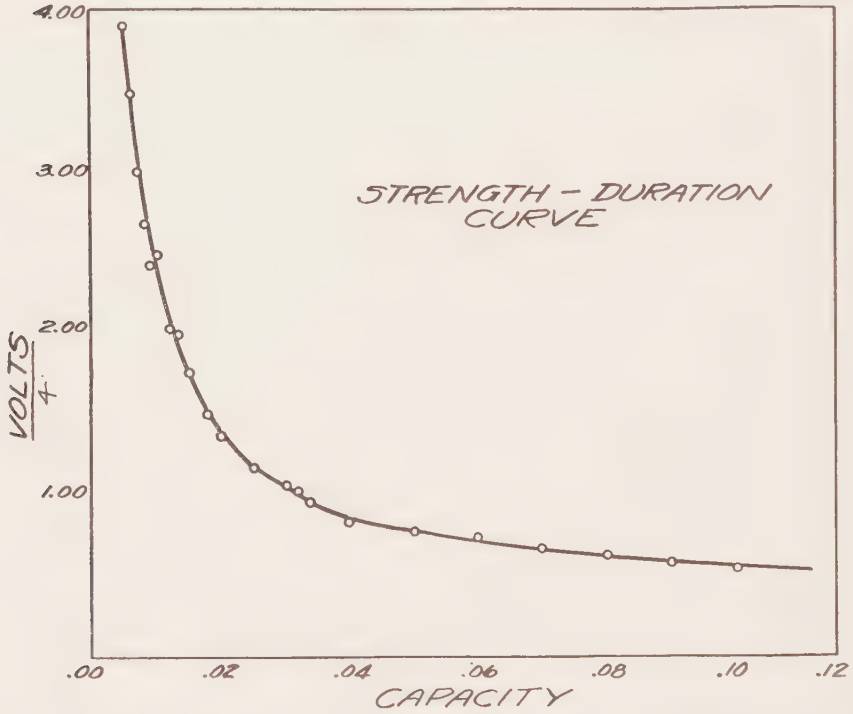

FIG. 23. A strength-duration curve of the sartorius muscle of the frog obtained by the author (condenser method) while in the Laboratory of the Sorbonne. Silver chloride electrodes; the complete absence of discontinuities is noteworthy.

chronaxie of the nerve without at the same time enhancing that of the muscle. Hypertonic saline augments the chronaxie of both (Laugier, *621*).

It follows from Lapicque's theory that a drug such as strychnine, which produces a block by diminishing the chronaxie of the nerve, should be counteracted in its action by a drug which diminishes that of the muscle. Experimentally it is found that veratrin, nicotine, and physostigmine

restore a nerve muscle preparation curarized by strychnine (*609*). Curare itself is likewise antagonized by physostigmine (*607*) and by nicotine (Langley, *586, 587, 588;* also Lapicque, *607*).

In Lapicque's investigations on chronaxie no evidence was found in muscle for the existence of Keith Lucas' β-substance. It was sought for with rectangular rheotome currents of short durations (Lucas method) as

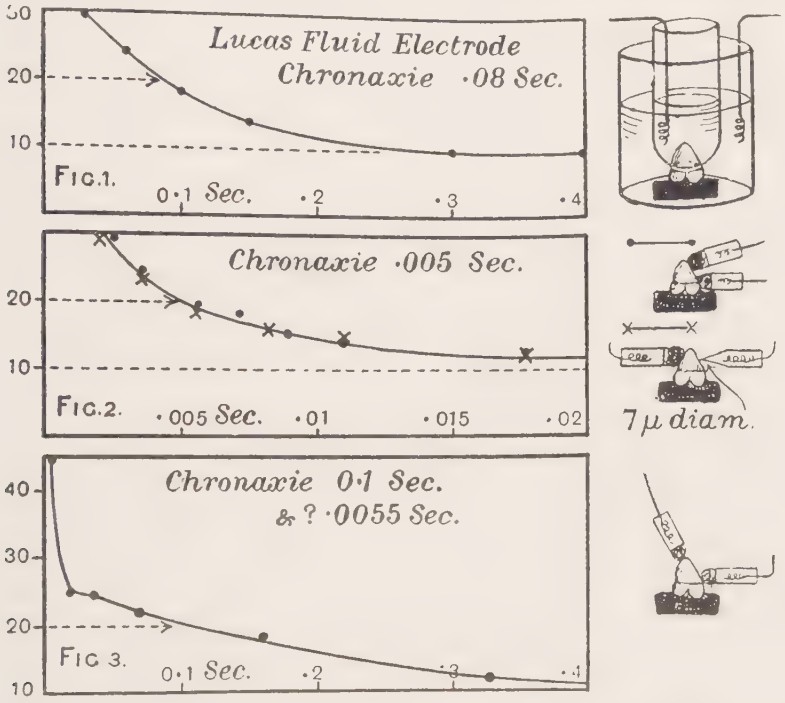

FIG. 24. Adrian's diagram showing the variations of the chronaxie of frog's ventricular muscle with the nature of the stimulating electrode. Current durations determined by Lucas contact breaker. Adrian's value, observed with the pore electrode (middle), approaches that obtained by Lapicque and Veil (3.5σ; *C. R. Soc. Biol., tom. 91*, 368) using the condenser method. (*Journ. Physiol.*, vol. 59, *Proc.* p. lxii).

well as with condenser discharges, yet in every case the strength-duration curves have been continuous (fig. 23). As Davis (*223*) and Adrian (*11*) have suggested (see fig. 24), this is probably due to the fact that Lucas employed large non-polarizable "fluid" electrodes on excised muscle. When the pore electrode is used (Davis) or any form of small metallic electrode, the evidence for the β-substance disappears. Lapicque believes, in view of the theory of iso-chronism, that the action current of the nerve excites

the muscle directly, without the intermediation of a junctional tissue, a view strongly upheld by Forbes (*330;* see Chapter VI below.)

When gross differences exist between a nerve and its effector, a single stimulus is ineffective, but repetitive stimulation may serve to overcome the barrier of the differing time relations. Thus vasomotor nerves may require to be stimulated 3 to 40 times before producing an effect (*600, 554, 193, 194*). Lapicque (*599, 606*) has applied this conception to the central nervous system to account for temporal summation. Bremer and Rylant (*153, 154*) have also adopted this conception as a working hypothesis to account for the action of strychnine on the central nervous system (see Chapter XVIII).

SUMMARY

The more general features of the electrical variations of excitable tissues may be described as follows. When galvanometer leads are taken from two points along the longitudinal axis of a muscle or nerve, uninjured and at rest, no current passes through the instrument. Activity or injury of a given region causes that region to become electrically negative to all other inactive, uninjured parts of the tissue. When a propagated disturbance passes along an excitable tissue, starting from its proximal end, the proximal electrode first becomes negative and then the distal electrode, and the result is a diphasic excursion of the recording instrument. This is the action current. Should the distal end be injured beneath the galvanometer lead, a similar propagated disturbance will pass beneath the proximal electrode but will not reach the second contact, and consequently the recorded action current will be *monophasic.* This then is the monophasic response, and its time course is believed to resemble that of each constituent electrofibregram of the muscle or nerve. The constant current which flows from an uninjured to an injured region is the current of injury.

The features of the string galvanometer records of action currents from various types of skeletal muscle are also described, and the consequences of irregularity in the arrangement of individual fibres explained.

The polarization theory of the causation of potential differences in irritable tissues is described, the essential feature being the assumption of the existence of a semipermeable membrane at some "fatty-aqueous" interface within the tissue.

The theory of the excitation-time characteristics (chronaxie) of irritable tissues is explained, and the significance of chronaxie determinations discussed. The chronaxie of various irritable tissue runs parallel with the magnitude of the latent period and with rate of conduction of the tissue.

CHAPTER II

On the Latent Period of Skeletal Muscle

PREVIOUS OBSERVATIONS

The extreme brevity of the interval between the stimulation of a nerve and the response of a muscle was noted by the earliest observers, including Whytt, von Haller and von Humboldt (see Introduction), but it was von Helmholtz (*457*) who first subjected the interval to accurate measurement (1850). By employing the electrical method of Pouillet he found that the tendon of the surviving gastrocnemius muscle of a frog responds within 10σ after direct application of an electrical stimulus.

Gad (*369;* 1879) later observed that after a given stimulus the individual fibres of a muscle respond within 5 or 6σ, and he suggested that part at least of the delay in von Helmholtz's experiment resulted from the inertia of the recording system and to elasticity of the inactive constituents of the muscle. Gad observed, for instance, that when the curarized sartorius muscle (parallel-fibred) is stimulated by an induction shock applied to its pelvic end, the recorded contraction,—the distal end being attached to the lever,—is preceded by a slight elongation. This was attributed to extension of the unexcited portion of the muscle which takes place at the moment when the excited part begins to shorten. Bethe and Happel (*97*) have recently confirmed this result and investigated it in detail using a wholly different method. By arranging the muscle itself (on which delicate silk threads had been placed) directly in the optical system they were able to photograph the actual movements of the surface of the tissue. They found that the commencement of elongation corresponds closely to the beginning of mechanical activity of the portion of the muscle directly stimulated.

One finds among many of the earliest investigators the belief expressed that the latent period of contraction of skeletal muscle is an artefact resulting from the inevitable inertia of mechanical records. Thus, as early as 1859, Harless (*436*) attributed the delay in von Helmholtz's experiment to the time required for the muscle to transmit its tensile response through the lever which broke the contact. He remarks that in any method of recording the latent period of shortening, many conditions are present which tend to delay the visible movement of the lever, and these may be responsible for the so-called latent period. Harless, however, was unable to obtain experimental foundation for his belief, and the least interval which he was able to observe was 18σ. A similar view was early maintained by Gad (*369*). He pointed out that the long latency commonly observed is due to the fact that successive elements in contiguous portions of the muscle, as they become contracted, stretch the inactive portions of the muscle so that no general shortening occurs until a large proportion of the total number of muscle elements are activated. He concludes from this, (1) that the mechanical latent period of the entire muscle must be greater

than that of the muscle elements, or, in other words, that the muscle is not activated simultaneously throughout its entire length, and (2) that the shortest latent period which it is possible to observe in the muscle as a whole probably is the nearest approach to the true latency of the individual muscle elements. Tigerstedt (*986*) came to a similar belief and drew the important conclusion that the apparent diminution in latency as the intensity of stimulus is increased (direct stimulation) is due to the more synchronous excitation of the individual muscle elements. Gad had concluded that the latency was probably as brief at room temperature as 4.5σ, while Tigerstedt obtained as his shortest latency the value of about 5.0σ (shortening); Bernstein (*89*, *90*) reduced it to 4.0σ.

Emerich Nagy v. Regéczy (*802*) went even farther than Gad and Tigerstedt and stated his belief that the commencement of contraction was probably synchronous with the stimulus. As with Harless, he was unable experimentally to confirm this suspicion but his work foreshadows the important recent investigation of de Jongh, Roos, and Einthoven. Yeo and Cash (*1065*) and Yeo (*1064*) examined the question critically (reviewing all the early literature with great thoroughness) but were unable to agree with the experimental results of Tigerstedt and Gad and they were furthermore unprepared to believe that the latent period may be reduced to nothing. Though they took many precautions to guard against instrumental delay, they were nevertheless unable to reduce their latencies to much less than 6σ, and in the majority of their experiments the latent period of shortening lay between 8 and 10σ. The tendency of recent work, however, has been to confirm the suspicion of Harless and v. Regéczy. It may be noted in passing that Tigerstedt expressed his belief, "that the mechanical latency of the muscle elements has a duration of the same order as negative variation, *i.e.*, not longer than 1σ."

Burdon Sanderson (*179*, *180*) concluded from his well-known experiment that mechanical thickening of a given spot of muscle occurs approximately 2.5 to 3σ after a stimulus applied at that spot. Owing to an unfortunate error in the published results of his work, he was widely quoted as having proved that the electrical and mechanical responses begin simultaneously. He had intended to state that the beginning of the electrical response occurs simultaneously with the application of the stimulus. The error found its way into many textbooks (Starling), but was very soon corrected by Burdon Sanderson (*181*) himself, and by Dürig (*250*), who for a short time worked under him.

The difference between the latency for nerve stimulation and stimuli applied directly was observed by many authors, notably Tigerstedt (*986*), Hoisholt (*495*), Dürig (*250*), Boruttau (*128*), and Burdon Sanderson (*180*, *181*). The observed values for this difference vary considerably, some authors (*181*, *1044*, *359*) finding it only 3 to 4σ, and others as high as 10σ (*36*, *495*). A review of these investigations is given by Burdon Sanderson in Sharpey-Schafer's Textbook (*181*). Snyder (*955*) determined the interval between the electrical response and the shortening of the tendon and arrived at a value of 7 to 8σ. Finally, Rauh (working under Garten) has found, by an ingenious optical method, that the thickening of a spot of gastrocnemius muscle at 17.5° occurs within 2.4σ after stimulation, and in some experiments this author observed values as low as 1.6 and 1.9σ (*797*). Somewhat higher values were reported by Steinhausen (*968*). Pratt and Eisenberger (*784*) have recorded the latency of an individual fibre by the mercury-drop method, obtaining a value of about 12σ, but, as they point out, the conduction time from the pore electrode to the spot recorded is in part responsible for this high value. Their records show very clearly a marked diminution of the latency with increasing strength of stimuli, showing the effect of cathodal spreading.

More recent (1923) investigations in this field are those recorded in a thesis by de Jongh (*528*). This author has expressed his belief that the moment of stimulation and the beginning of the mechanical response of heart muscle are in fact simultaneous, as Harless originally suggested, and as Burdon Sanderson had inadvertently stated. For recording the mechanical response, de Jongh used what he has called a "hair" myograph ("Snaarmyograaf"), which is built upon the torsion-wire principle with very high magnification, and is devised to record directly the thickening

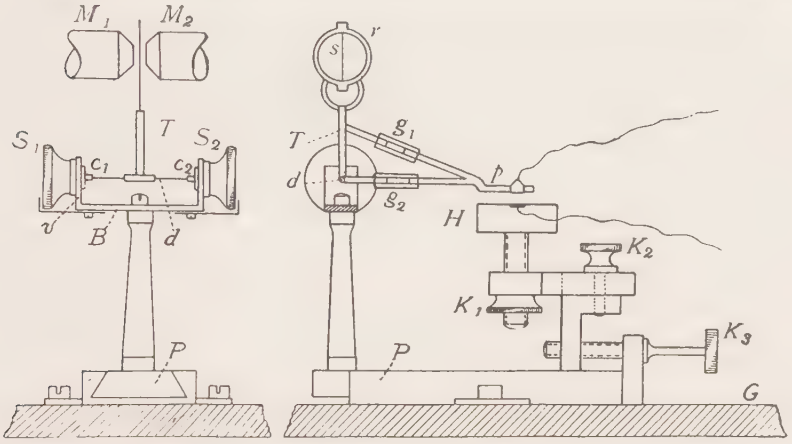

FIG. 25. A diagram of the "snaarmyograaf" used by de Jongh (*528*) and by Roos. The muscle lies on the support, *H*, in which the anode of the stimulating circuit is imbedded. The arm, *p*, carries the cathode and serves to deflect the hair, *s*, when thickening of the muscle occurs. When naturally beating heart muscle is employed, the two electrode contacts may be used to lead off to a galvanometer. In this way simultaneous electrical and mechanical records are obtained. The whole triangle, Tg_1g_2p, is mounted upon a torsion wire, *d*, 5 cm. long and 0.5 mm. thick, whose tension is regulated by the two screws, S_1 and S_2. The fine hair, *s*, is in an optical system similar to that of a string galvanometer and thus a magnification of 1000 times can be obtained. The diameter of the hair is 3 to 4μ (*i.e.*, of the order of magnitude of a galvanometer string).

of the exact spot of muscle stimulated (see fig. 25). The stimulus may be delivered by the arm of the myograph which lies on the muscle (cathode), or the contact may be used to lead off to a galvanometer. The instrument is believed to possess the same degree of accuracy as the galvanometer string. One of de Jongh's records is reproduced in figure 26.

Erlanger and Gasser (*287*, p. 657) have shown that the action current of nerve in response to a slightly over-maximal stimulus begins not later than 0.06σ after the stimulus is applied. Their diagram illustrating this

fact is reproduced in figure 27. The interval between the stimulus and the electrical response ("utilization period") is therefore of the same order of magnitude as the duration of the stimulus, and is so brief as to be far beyond the limit of experimental error of ordinary recording methods. Since this is true of nerve there is no reason for believing that it is not also

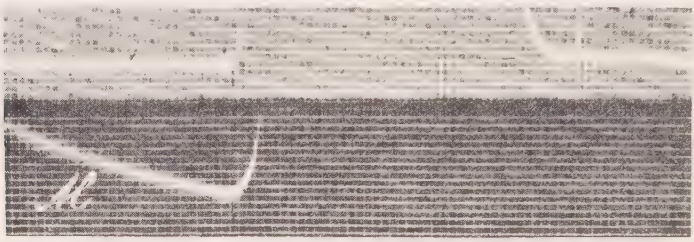

FIG. 26. A simultaneous record of the electrical and mechanical responses of a naturally beating heart (de Jongh, *528*) obtained with the "snaarmyograaf."

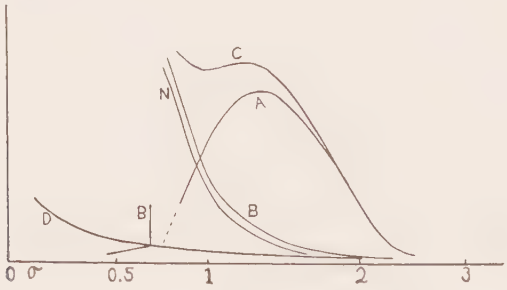

FIG. 27. The action current of nerve as disclosed by the cathode ray oscillograph. The action current (*A*) in this figure was obtained from beneath the stimulating electrode (the electrode and the "lead" were one and same), having been derived from the combined curve, *C*, which is the action current as modified by the "escape" of stimulating current. *B* shows the moment of stimulation, and *N* the descending curve of current "escape." Note that the ascent of *A* is *not* sigmoid, that the duration of the rising phase is about 0.5σ and that the total duration is not more than 1.4σ. Temperature 22°. (Erlanger and Gasser, *Amer. Journ. Physiol.*, vol. 70, p. 657.)

true of muscle. The observation of Erlanger and Gasser (*287*) thus confirms Burdon Sanderson's inference that the stimulus and the electrical responses are approximately simultaneous. de Jongh's conclusion that the stimulus and the beginning of mechanical response are simultaneous amounts, therefore, to a complete denial of the existence of a latent period.

It will be seen from this brief preliminary account that as mechanical

recording instruments have been improved the latent period of skeletal muscle has become progressively smaller until it would appear to have been reduced to nothing. In this chapter we shall consider de Jongh's conclusion in the light of other recent observations on the latent period of intact skeletal muscle, considering especially the relation of the latent period to the beginning of the electrical response.

THE FOUR PHASES OF THE LATENT PERIOD (OF CONTRACTION)

The interval between the instant of stimulation of the nerve and the commencement of mechanical shortening of the muscle appears to be divisible into at least four distinct phases (*359*). These are most readily studied by obtaining simultaneous records of the electrical and mechanical responses of intact muscle stimulated indirectly. For satisfactory measurement of these four phases of activity scrupulously accurate mechanical records are necessary and the condition of the recording muscle must be as nearly normal as possible. The four phases are: (1) The conduction time of the motor nerve; (2) the delay at the motor end-plate; (3) a period following the beginning of the muscle action current during which mechanical properties of the muscle remain apparently unaffected by the stimuli. This has been termed the "true latent period;" (4), a period of rigidity, during which the muscle, though affected by the excitation, does not shorten appreciably. We shall consider these four periods in the order given, and the reader will be aided in following the description by reference to figure 30, p. 98.

Conduction time. The rate of propagation of the motor nerve impulse in the green frog (*Rana temporaria*) at room temperature is, as is well known, approximately 30 meters per second. This, the original value assigned to it by von Helmholtz (*457*), has recently been confirmed with more accurate technique by Erlanger and Gasser (*287*) and others (*660, 774*). The average conducting distance, measured from the cathode to the equator of the recording muscle, was, in the majority of experiments, about to be recorded approximately 3 cm. The conduction time in this length of nerve would, accordingly, be only 1σ. The interval, however, observed between the moment of stimulation and the action current was on an average 4 to 4.5σ at 20° (English *Rana temporaria*).[1] This, therefore, points to a delay at this temperature of at least 3σ somewhere in the conducting system. It is conceivable that the delay might occur in setting up of the nerve impulse, but Erlanger and Gasser (*287*) have shown conclusively that this delay is less than 0.10σ, which would be smaller than the

[1] References to my own investigations on "frog" muscle refer always to this species.

limits of experimental error. Moreover, owing to the "wandering" of the cathode (see Kato, *541;* also Schellong, *850*, Samojloff, *838a*, Chapter VIII) with over-maximal stimuli, 1σ is probably a slight over-estimate of the actual conduction time. The other alternative, therefore, is that the delay occurs in the region of the neuro-muscular junction.

End-plate delay. Samojloff (*840*) has recently devised an ingenious method for measuring the end-plate delay. He has taken the proximal galvanometer lead from the sciatic nerve at its point of entry into the gastrocnemius muscle and his distal lead from the tendon of the muscle (excised; see fig. 22, Chapter I). Under these conditions he finds that the nerve impulse produces a small initial deflection, and the electrical response of the muscle a larger second deflection, the first portion of which is, as we have seen, in the downward direction similar to the Q wave of the electrocardiogram. The interval between the beginning of the action current of the nerve and that of the muscle corresponds roughly to the end-plate delay. It is complicated, however, by the conduction time from the point of entry of the nerve to the equator of the muscle. The method, however, is more direct than the one which has been employed in the course of the present investigation. The intervals determined, however, are at room temperature approximately the same whichever method is used (*i.e.*, 3 to 4σ).

The delay at the motor end-plate might be due to slower transmission in this region, or it might be due to some more fundamental delay in the setting up of the action current. It is likely, for many reasons, that the action current, whether in nerve or muscle, follows at an interval not greater than the duration of the exciting stimulus. According to the membrane theory of conduction as elucidated and modified by Nernst (*731*), Lapicque (*595*, *601*, *604*, *605*), Hill (*470*), Lillie (*645*), Forbes (*318*, *325*) and others (*224*, *228*, *522*), immediately an adequate local concentration of ions occurs at the polarized interface of nerve or muscle, the wave of permeability responsible for excitation commences.

We have seen that the effective duration of an induced shock may be very brief, *i.e.*, of 0.10σ or less (*386*, *287*). Now the duration of stimulus necessary to set up a concentration of ions adequate for excitation is a function of the intensity of the stimulus. When this intensity is just double the threshold for a given excitable tissue, the duration of current necessary for excitation is referred to as the "chronaxie" (Chapter I) or excitation time (Lapicque, *598;* Lucas, *659*). It follows from this that when a constant current of double the threshold intensity is delivered to a nerve or muscle, an action current is produced after an interval not greater than the chronaxial value of the stimulated tissue. This deduction has not

as yet been thoroughly substantiated experimentally. One knows, however, that action currents do occur at very brief intervals following excitation by an induction shock, intervals briefer actually than the chronaxie of the tissue, but unfortunately in the experiments in which these determinations were made the stimuli were not graduated in terms of threshold intensity and duration. Experiments were made (by the writer) with the galvanometer technique to test this assumption, but the action current actually appeared synchronously with the exciting stimulus. This is due in part at least to escape of current, and as the interval sought for was in any case brief, it was decided that the galvanometer technique would not yield results of experimental value. If one assumes for argument that the inference is correct, the delay in the appearance of the action current at the end-plate, owing to the chronaxie of the tissue, would not be more than 0.30 to 0.50σ, since this is the chronaxial value usually assigned to the gastrocnemius muscle fibres of the frog (Lapicque). However it does not necessarily follow that a nerve action current *is* of double the threshold E.M.F. necessary for excitation of its muscle, and if less intense it would require a longer utilization period to set up an adequate concentration of ions at the muscle interface. Even with this in mind it is difficult to account for the observed delay of 3 and sometimes 4σ, and one must, therefore, search for other sources of delay. Slow conduction in the small terminal branches of the nerve in the region of the end-plate might be urged, or time lost in the passage through some hypothetical junctional tissue such as the β-substance of Lucas. On a priori grounds the case for slowed conduction in the terminal regions of the nerve fibres is very strong; for, other things being equal, the rate of conduction diminishes with the diameter of a nerve fibre (Lapicque et Legendre, *611, 612;* Göthlin, *399, 400;* Lillie, *645*). This has recently been established quantitatively by Gasser and Erlanger (*378a*), who have demonstrated that the velocity of conduction is a linear function of fibre diameters in a mixed nerve.

A related question has recently been treated by Forbes, Ray and Griffith (*330*, p. 590). They found a relatively large delay occurring at the myoneural junction for the second of two stimuli separated by a brief interval, *e.g.*, when a nerve is stimulated twice at an interval of 3 to 4σ, the muscular responses not infrequently were separated by as much as 6 to 7σ (frog), and these authors were careful to show that this delay did not occur in the nerve trunk owing to slowed conduction of the second impulse (slowed conduction of the second impulse did occur in the nerve trunk if the interval between the two stimuli was less than 4σ). Forbes and his collaborators suggest that it is due to the refractory period of the muscle, which prevents it from responding sooner, and they emphasize that if this is true "the nerve impulse has the power to excite the muscle for a time after its moment of arrival at the neuromuscular junction, either by virtue of its own duration, or through some special activity to which it gives rise at the junction" (*330*, p. 615), but since the

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first response is also delayed 3 to 4σ, it would seem likely that there is a common cause for both delays, which in the case of a first response could not be attributed to the refractory period. Since the rising phase of the action current in frogs' nerve is only 0.4 to 0.6σ in duration (Erlanger and Gasser, see fig. 27), it seems difficult to invoke the physical duration of the action current to explain the delay, and it suggests the possibility of a slowing of conduction somewhere in the region of the nerve termination. The assumption of a delay caused by a specialized junctional substance appears unlikely, for the evidence which Lucas (*659*) put forward for the existence of such a specialized material (the β-substance) has recently been called in question by many authors (*223, 330, 521, 597, 603*).

If the nerve endings themselves, as distinct from a hypothetical junctional substance, conduct more slowly than the nerve trunk it is important, as it would probably account for the apparent differences in time relations (of action current) between motor nerves and the muscles which they innervate. Thus, certain authors (*137, 659, 737, 1031*) have found that some muscles do not, as is demanded by the theory of iso-chronism (p. 81), have the same chronaxie as their motor nerves. Now the duration of the rising phase of the action current, which varies roughly as the chronaxie, probably determines whether a nerve can stimulate a muscle or not,—provided of course the E.M.F. of the action current is adequate. There is considerable difference between the duration of the rising phase of nerve action currents and of the action currents of muscles,—a condition, which in Lapicque's terminology may be designated "action-current heterochronism." If the conduction is slowed in the motor termination, it is likely on the basis of Lillie's hypothesis that the duration of the rising phase of the action current of the motor nerve termination would be increased, and in this way the gap may be bridged between the differing time relations of the action currents of nerve and muscle. There is nothing in the observations on the delay at the motor junction which is essentially out of harmony with this view.

I have frequently noted that in *fatigued* muscle in which the duration of the rising phase of the action current is greater (cf. also, *248*) than in a fresh muscle. the end-plate delay may be as great as 4 or 5σ, instead of the usual 3σ, which is in keeping with this view that the time to maximum of the action current and the end-plate delay vary together.

Wieser (*1044*) who worked under Garten, has also examined the influence of fatigue on the end-plate delay. He performed two series of experiments in one of which he examined the influence of the "fatigue time" and the other the "Zwischenzeit." In the first series the muscle was stimulated for various time intervals and at a constant interval ("Zwischenzeit") the same preparation was again stimulated by a single twitch and the end-plate delay determined. He found that it increased strikingly with the duration of the fatiguing stimulus ("Ermüdungsdauer"). Thus, in one experiment

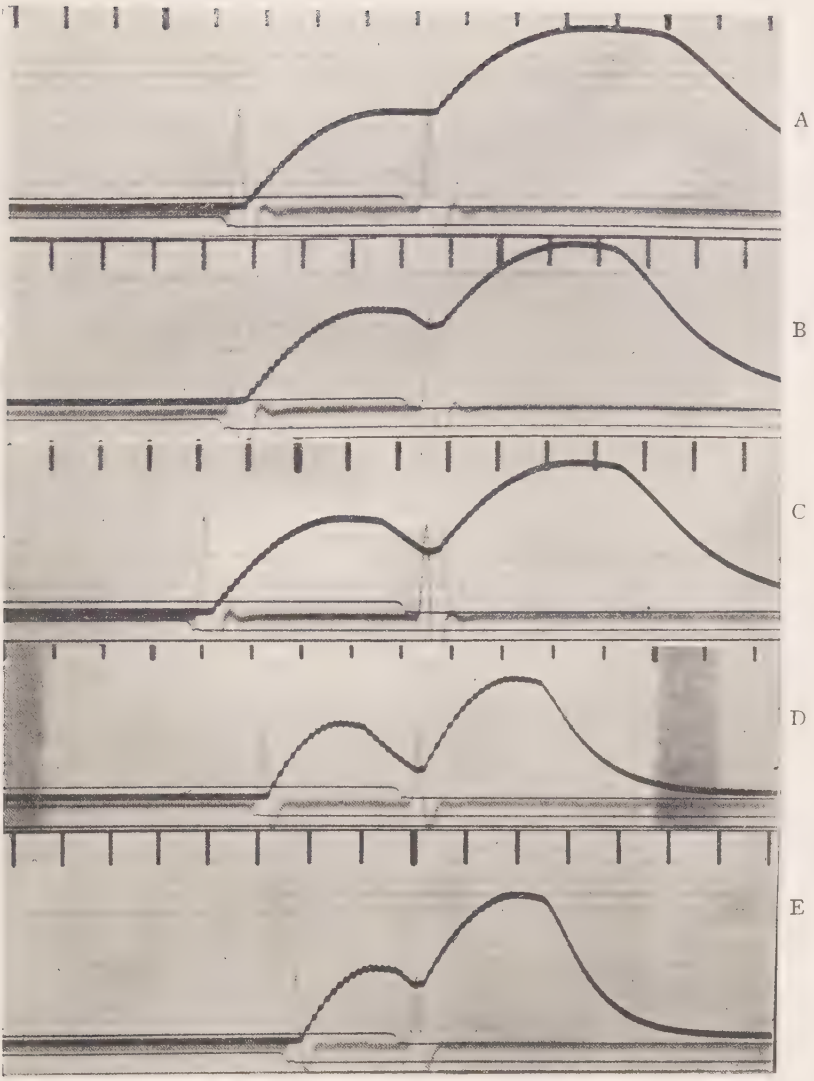


FIG. 28. Responses of intact gastrocnemius to single stimuli at varying intervals, showing the phases of the latent period. Myograph frequency 460 per second, to be seen in the record. Moments of first and second stimuli indicated by signals below and above galvanometer string. 3 cm. vertical distance = 625 grams tension, as reproduced (reduced by one-fourth). Time = 0.02 second. Lowest horizontal line = zero tension (seen only in D).

A. $T = 16.5°$; response II occurs near the end of the plateau of response I.

B. Response II occurs just after the "angle" of I. The period of rigidity as evidenced by a slight upward movement of the myograph before shortening is to be seen in both the first and second responses.

C. Same as B, with a slightly greater interval.

D and E. Same preparation at 23.5°. The period of rigidity is well marked in E.

after fatiguing the muscle for 1 minute, the end-plate delay which previously had been 5.7σ, arose to 10.0σ—a difference of 4.3σ. In some experiments differences as high as 6.6σ were observed. In a second series of experiments he fatigued the muscle during a constant period, subsequently stimulating it by a single twitch at varying intervals (thus varying the "Zwischenzeit") after the fatiguing stimulus. In the latter experiments he found that the end-plate delay recovered from the fatiguing stimulus with considerable rapidity, and in a fresh preparation might recover from fatiguing stimuli of one second duration, within two to three seconds. It is clear from this that fatigue causes a marked augmentation in the end-plate delay.

Another way of accounting for the increased duration of action currents of muscle above those of nerve emerges from the structural considerations brought forward by Tiegs (*980*, *981*). According to this author the polarized interface of muscle is to be identified with his helicoid membrane, which he believes to characterize the structure of all skeletal muscle fibres. If this is so, the action current as it spreads along the fibre must pursue a spiral course, which would give to the action current when led off in the ordinary way an apparent enhancement of duration. This possibility cannot, however, be given full consideration until Tiegs' morphological results have been amply confirmed.

To summarize: the so-called "end-plate delay" is most likely due to the slowed conduction in slender terminal branches of the motor nerves. Fatigue of the muscle leads to a pronounced augmentation of this delay.

The "true" latency. Careful inspection on an accurate record of the interval between the electrical and the mechanical responses reveals the fact that the myograph often moves upward very slightly (at 20°) during a period of 4 to 5σ before mechanical shortening commences (*259*). This one may see in the first response of figure 28 B. Shortening itself always commences abruptly, as may also be observed in this figure, but in the single response it is quite impossible to determine at what point the muscle is first affected by the stimulus. When, however, a second response occurs during relaxation of a first, the period following the second action current during which the muscle is *unaffected* by the stimulus may be determined with great accuracy, for at an interval of 2 to 2.2σ (fig. 28, B, E) after the commencement of the second action current the muscle ceases to relax, and there follows in the record a flat interval during which the relaxation is checked. The interval between the action current and the first manifestation of mechanical activity as disclosed in this way has been designated the "true" latency.

In the measurement of the "true" latency, several sources of possible error are involved: (1) Instrumental lag; but this is as low as 0.3σ, which is near the observational error. (2) Conduction time of the wave of increased tension through the inactive tendinous parts of the muscle; but this has been minimised by having the muscle initially at high tension so that the extensible portions of the muscle are already taut; moreover, temperature alterations, presently to be described, indicate that this source of error is a small percentage of the total interval. (3) Another source of error is imposed by the fact that the fibres respond only within 1σ of each other throughout their length (p. 106, above). When a muscle is under tension, presumably the activity of the fibres or parts of fibres first to respond will be reflected immediately in the mechanical response (provided the muscle is relaxing). The beginning of the period of rigidity has accordingly been taken to represent the *first* fibres thrown into mechanical activity within the muscle. This will be referred to again below.

It is unlikely that the instrumental lag under these circumstances, together with any other sources of error, require a deduction from the observed latency of more than 0.5σ (*259*). If corrected to this extent, the "true" latency of a muscle at 20° becomes 1.5σ. When the mechanical thickening is recorded by the *Snaarmyograaf* the interval between the moment of application of the stimulus and the first thickening of the muscle is also approximately 1.5σ for both the sartorius and gastrocnemius muscles. Investigations upon the latent period have been made with this instrument in the laboratory of Professor Einthoven by Dr. Roos (*820*), who was kind enough to communicate certain of his results to me before their publication, and to permit me to refer to them. It is therefore evident,—since the electrical response begins in a skeletal muscle synchronously with a direct stimulus,—that the first mechanical alteration follows at an extremely brief interval after the commencement of the electrical response, and *this interval is the same whether thickening is recorded, or whether it is determined from the responses of the tendon, by the method just described.*

The period of rigidity. Following the period of "true" latency as observed in the second response occurring in the course of relaxation from a first, the lever of the myograph becomes stationary or deviates slightly upward for a period of approximately 4σ, showing clearly that the muscle has been affected by the stimulus and suggesting that it becomes fixed or "rigid" previous to shortening (*259*). Such a "period of rigidity," as it has been called for want of more accurate knowledge of its intimate nature, might be caused in one of several ways. That it is not merely the resultant of two opposing forces, is evident from the following considerations: (1) the slight upward deviation of the myograph before shortening is often seen in a first response where there is no contrary force such as exists in relaxation; (2) it occurs similarly when the second stimulus falls near the end of the plateau

of a first, where again there is no opposing force; (3) the interval between the electrical response and the shortening (which includes the period of rigidity) is the same for a first stimulus as for a second (6 at 20°); (4) the *precise angular character* of the beginning and termination of the period of rigidity when determined with an accurate myograph (see fig. 28), leaves little doubt as to the abrupt nature of the processes which give rise to it. When determined on fatigued or excised muscle, the precise "angles" denoting the beginning and cessation of the period of rigidity, which with fresh muscle are so exact, become rounded and therefore incapable of accurate analysis.

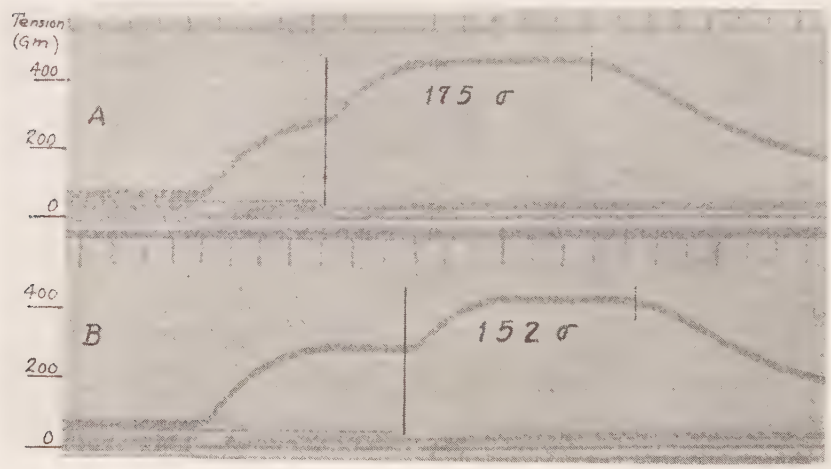


FIG. 29. Responses of the intact soleus of a cat to single stimuli at varying intervals. Note the shortened character of the period of rigidity when response II falls early in the plateau of response I. (Cobb and Fulton, unpublished.)

Several points concerning the period of rigidity have been observed since it was first described (*259*). Though always the same in duration when occurring at any point *after* the "angle" of a first response, it is of greatly diminished duration when occurring a few sigmata *before* the "angle" of a first response, and its duration appears to become less and less as it occurs earlier and earlier in the course of a first response. This is particularly striking in the responses of the soleus of the cat (fig. 29) and it has been found to hold true also for the gastrocnemius of the frog, and for all other muscles in which it has been measured (*e.g.*, vastocrureus of the the cat).

This raises the question of the *significance* of the period of rigidity. The practical outcome of the recognition of the period of rigidity is that it

clearly accounts for the discrepancy in the duration of the latent period as determined by the method of thickening, on the one hand, and of recording the shortening of the tendon on the other. Why it occurs is another question. Though outspreading of excitation (*13*) from the nerve ending may be a contributing factor in accounting for the period of rigidity, it cannot be wholly responsible since the average length of fibre in gastrocnemius is about 12 mm. (*84, 696*) and the muscle conduction time over half this distance would be little more than 1σ (at 4 to 5 m. per second). That the period is not due to the taking up of slack of the tendon is evident from the fact that it occurs and is of the same duration at all initial tensions. Elastic "give "of the (taut) tendon can be largely ruled out as a explanation since the period of rigidity still occurs (unaltered in duration) when the tendon is practically excluded by attaching the muscle to the myograph by a ligature around the base of the tendon. It would appear, therefore, that the period is one in which the muscle attempts to shorten but is unable to do so, probably because it encounters some impediment. The impediment might be either internal, *i.e.*, existing within the substance of the muscle, or external in origin, *i.e.*, in the surroundings of a muscle. That the source of the impediment is chiefly internal, is evident from the fact that the period of rigidity still occurs in a muscle fully isolated from all external frictional resistances of skin and fascia, when the initial tension on the tendon is negligible. Very sensitive levers have been used to test this and one capable of showing a tension of less than 0.1 gram failed to disclose any tendency towards a shortening of this period. Though in the intact muscle the external resistances may be of some slight consequence, it is more probable that *internal* impediment is the chief factor in the production of this period. We may therefore direct our attention to the possible sources of internal resistance.

Let us use as a working hypothesis the illuminating view put forward by Gasser and Hill (*390*), that the contractile elements of a muscle are to be considered as an elastic network bathed in a viscous medium (Chapter IX). Whatever theory of muscular contraction one adopts, structural considerations must be taken into account, and it is difficult to conceive of a muscle fibre changing its shape without the intermediation of movement of fluid substances, probably highly viscous in nature, through a myriad of microscopical channels (Nicolas Steno). The viscous resistance offered to such a movement of fluid must be of great magnitude. It would appear highly probable, therefore, that the period of rigidity represents one in which the contractile elements of the muscle are attempting to counteract the impediment of their own viscous surroundings. When they

have done this and are therefore maintaining the tension which they themselves have developed, a second stimulation will cause them to shorten further, but they will not have initially as great an impediment to counteract as in the case of the first contraction. When, however, relaxation commences and the tension is necessarily thrown again on to the viscous and passive elements in the muscle (Chapters III and IV), they must again repeat the process of overcoming the viscous resistances. Along such general lines as these one may account for the occurrence of the period dur-

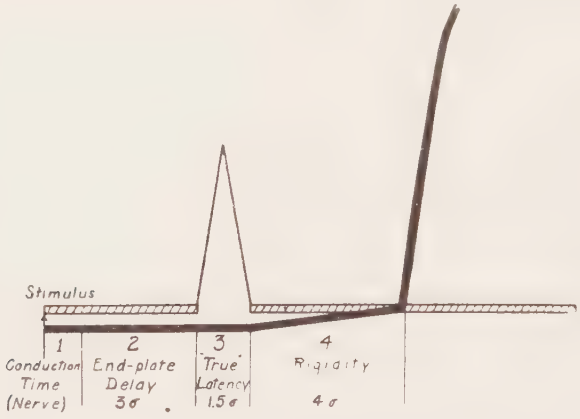


FIG. 30. A diagrammatic representation of the four phases of the latent period of an intact frog's gastrocnemius muscle at 20°C. stimulated through its nerve at an average conducting distance of 3 cm. The conduction time, assuming a rate of 30 M. per second, is therefore 1σ. The interval of "true" latency has been corrected by 0.5σ for instrumental and other errors. The durations of intervals 2, 3, 4 are indicated in the figure. Interval 4 (rigidity) was determined from measurements of second responses as explained in the text. String of galvanometer above; myograph below. The duration of the rising phase of the electrical response as shown in the diagram (0.75σ) is possibly somewhat too brief. (From *359*.)

ing relaxation and its failure to be as pronouced in the kinetic phase of a first response.

One need not, however, assume a constant viscous factor, for Gasser and Hill have reported rapid *changes* in viscosity[2] during the early stages of contraction, which, interacting with the rise of internal tension may be the cause of the *abrupt* onset of external tension (see figure 8 of *360*).

The four phases of the latent period of the response of a gastrocnemius muscle of a frog at 20° are shown diagrammatically in figure 30.

[2] For further discussion of muscle "viscosity" see below, pp. 248–252.

It is interesting to compare the absolute values of the four phases in the period of latency obtained in the frog with those observed by Liddell and the writer in the case of a mammalian muscle ($\pm 35°$). In the latter, the four phases do not occupy much more than 4 to 5σ. The end-plate delay is of the order of 1σ, and "true" latencies have been observed which were so brief as to be difficult of accurate measurement (*i.e.*, 0.5 to 0.6σ; fig. 79). The period of rigidity was usually 2 to 3σ.

THE INFLUENCE OF TEMPERATURE UPON THE PHASES OF THE LATENT PERIOD

Since we have found it justifiable to separate the latent period of shortening into four distinct phases, it is a matter of some interest to examine the effect of temperature upon each separate phase. The results of a series of

TABLE 2

Averages of the temperature coefficients of the four phases of the latent period in five experiments

Q_{10} latent period

EXPERIMENT	INTERVAL	PHASE I (ASSUMED)	(2) END-PLATE	(3) "TRUE" LATENCY RESPONSE II	(4) RIGIDITY RESPONSE II	(3 AND 4) TOTAL E. M. INTERVAL RESPONSE I
22.X.24	12–22°	1.79	1.32	2.00	1.51	1.75
13.X.24	11–21	1.79	1.30	1.89	1.54	1.71
15.X.24	10–20	1.79	1.50	2.15	1.36	1.70
24.X.24	10.5–20.5	1.79	1.56	2.47	1.50	1.75
2.XI.24	10–20	1.79	1.35	2.26	1.47	1.74
Sum.....			7.03	10.67	7.39	8.65
Average.....		1.79	1.40	2.13	1.48	1.73

experiments in which this question was considered have recently been described in detail (*363*). We may accordingly confine our discussion to the chief points which were disclosed in this investigation. By averaging relatively large numbers of observations (always from the same preparation) at two temperatures differing from each other by 10 degrees, it was found that the Q_{10} had a characteristic value for each phase of the latent period over the relatively restricted interval of 10 to 20° or thereabouts. The results of five typical experiments (each value given being the average of 10 to 12 observations at a given temperature) are summarized in table 2. The Q_{10} of the rate of conduction is assumed to be 1.79, the value established by Lucas (*660*). It will be seen that the delay at the motor end-

plate is but slightly affected by a change of 10°, the Q_{10} being about 1.40. The "true" latency, on the other hand, was found consistently to have a

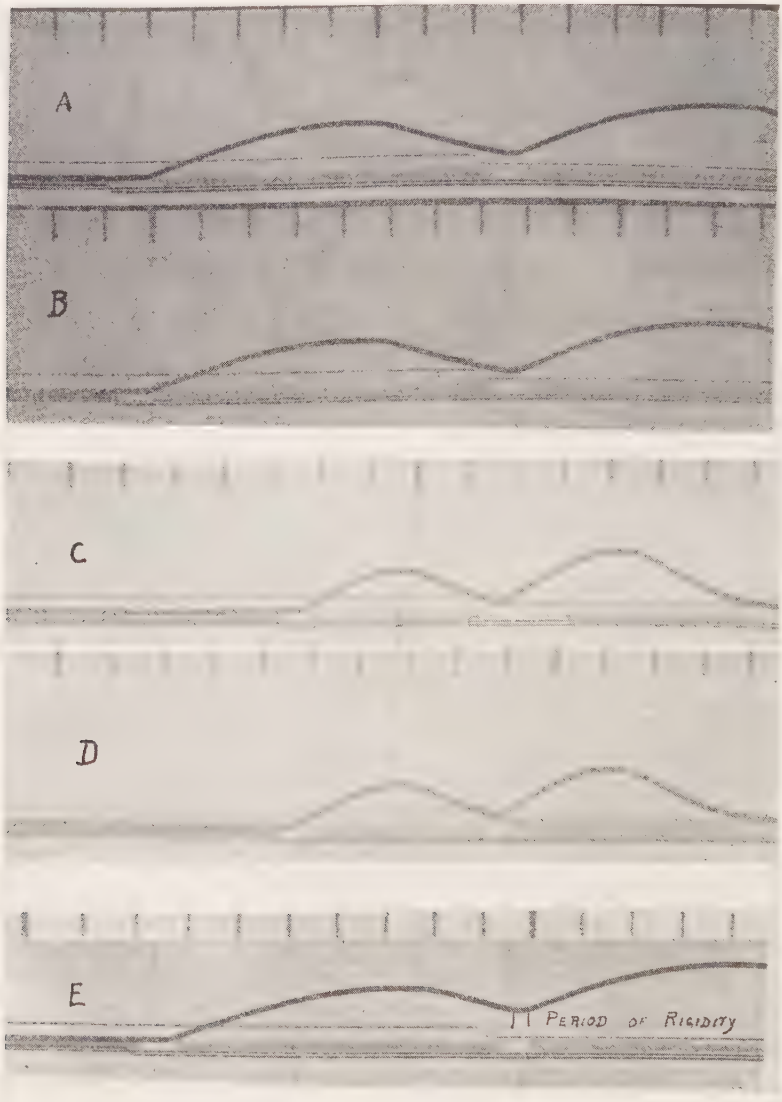


FIG. 31. Responses at various temperatures showing the effect of temperature on the latent period. Upper records (A, B) 12°; lower (C, D) 22°; the lowest record (E) is more favourable for the determination of the period of rigidity.

high Q_{10}, the average being 2.13. Kleinknecht (*547*) has also obtained a value of this order of magnitude for the interval between the electrical response and thickening, an interval which corresponds to the "true" latency. A value of approximately 1.50 was usually observed for the period of rigidity. If one averages the Q_{10} of the "true" latency plus the rigidity, one then obtains a summated coefficient of 1.73, showing how two apparently distinct processes may, if not properly distinguished, give an intermediate value from which it is impossible to draw satisfactory inferences. Records obtained in these experiments are shown in figure 31.

The chief point of discrepancy between these observations and those previously reported by other investigators lies in the low value for the end-plate delay. Samojloff (*840*), for instance, observed a Q_{10} for this phase

TABLE 3

Duration of the conduction time (over an average of 3.0 cm. of nerve) plus end-plate delay in the intact gastrocnemius of a decerebrate frog at temperatures ranging from 0° to 24°C. Preparation in Dewar flask partially surrounded by Ringer's solution containing 1 per cent gum arabic

	TEMPERATURE							
	0	4	8	[10]*	12	16	20	24
Duration (0.001 second)	13.0	11	7.5		6.0	5.5	4.5	4.0
	13.0	10	8.0		6.5	5.0	4.5	3.7
	12.5	10.5			6.2		4.7	3.8
Average	12.85	10.50	7.75	[7.0]	6.25	5.25	4.60	3.85
	$Q_{10}(0–10°) = 1.84$				$Q_{10}(10–20°) = 1.52$			

* Interpolated value.

of 2 to 2.6. I can offer no explanation for this apparent discrepancy other than the differing experimental conditions under which the respective observations were made. We have seen that excised muscle has a longer end-plate delay than intact muscle, and it is possible that the inevitable progressive deterioration of surviving tissue may be in part responsible for Samojloff's high value.

The low value for the Q_{10} of the end-plate delay has been further substantiated in a series of experiments in which observations were taken at intervals of 4° from 0° to 24° (Centigrade). The same preparation was used throughout and control observations were made at the end of the experiment (reversing the temperature) to guard against deterioration. The results obtained in a typical experiment of this sort are summarized in

table 3. It will be seen that while the Q_{10} for the interval 0° to 10° is 1.85, that for 10° to 20° is 1.52. The latter value is but little higher than that obtained in the first series of experiments over the limited range temperature, 12° to 22°. When the reciprocal of the absolute temperature is plotted against the logarithm of the velocity (according to the Arrhenius formula), it will be seen that the points do not fall in a straight line (fig. 32).

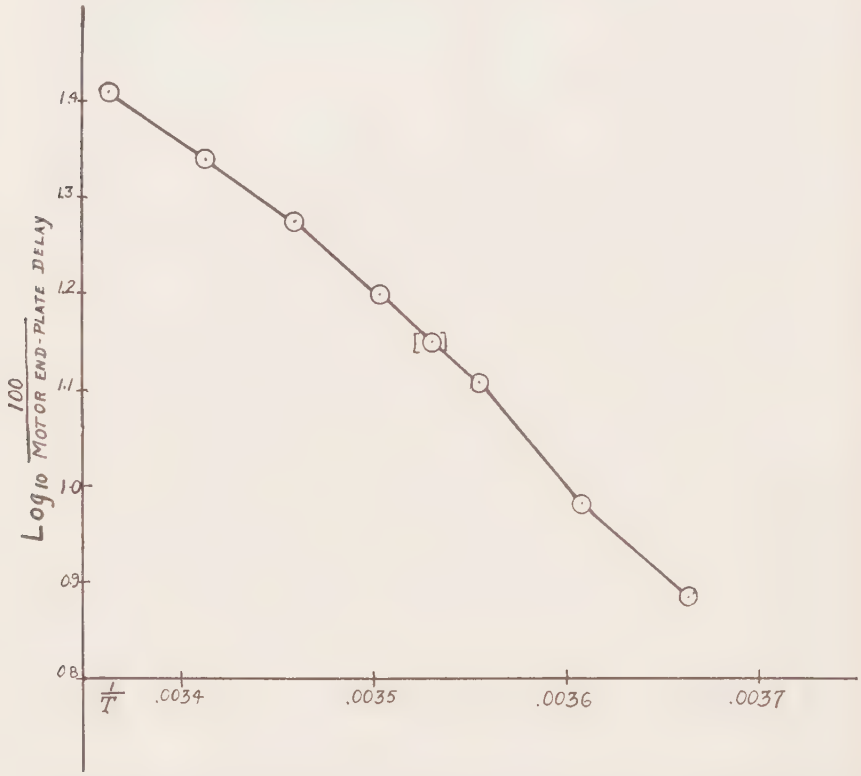


Fig. 32. The logarithm of the reciprocal (to obtain the velocity) of the end-plate delay plotted against the reciprocal of the absolute temperature. Not corrected for conduction time.

The critical thermal increment, μ, is therefore inconstant. The significance of this result has been discussed elsewhere (*363*). It suggests that we are not dealing with a single process (see Chapter III). However this may be, the curve remains of practically the same shape even though one deduct the conduction time.

The low value which I have consistently found for the Q_{10} of the end-plate delay favours the inference drawn from other evidence that the cause of this delay is due to a slowing of conduction in the terminal regions of the nerve (rather than to chemical processes), for the speed of nerve conduction has also a low Q_{10} (1.6-1.8; Lucas). In general Q_{10}'s are higher in isolated tissue, owing to progressive deterioration, than in tissues nourished by a normal circulation; consequently it is possible that the Q_{10} of intact nerve is lower than Lucas's average of 1.78, and if so would harmonize more closely with the Q_{10} of the end-plate delay of a decerebrate frog.

The high value (2.1) for the "true" latency, which we observed in both series of experiments (Q_{10} of 10° to 20°), is of importance for two reasons: (1) Since the interval varies markedly with temperature it shows that it is not an instrumental artefact, for the temperature of the recording instrument remained constant (Klienknecht). (2) If it is legitimate to make inferences as to the nature of the process from the value of its Q_{10}, the figure, 2.10, suggests that the underlying process is chemical and not physical.

THE SIGNIFICANCE OF THE ("TRUE") LATENCY OF SKELETAL MUSCLE

Einthoven (*270*), de Jongh (*528, 529*), Roos (*820*), and Lewis (*629*) are all of the opinion that when recorded with instruments of precision and due allowance for all sources of experimental error, the latent period of mechanical activity is so brief that the stimulus and the beginning of the mechanical response may be looked upon as being practically simultaneous. There is no doubt as to the facts, for, as we have seen, reliable observations have been made which show that the period of "true" latency may be as brief as 1 or 1.5σ (*797, 820, 359*), and the question is whether this interval is so brief that it may be disregarded. In mammalian muscle the interval is even less, but the fact remains that there *is* an interval, though extremely small, between the beginning of the electrical response and the beginning of the mechanical response, and that no one has ever been able to show that the two *do* actually begin with absolute simultaneity, or that the mechanical response ever occurs before the electrical. This suggests the existence of some important causal relation between the beginning of the action current and the mechanical response.

The estimate for the duration of the "true" latency (1.5σ) reached in the course of this investigation happens to coincide approximately with the duration of the rising stage of the action current, as estimated by Lucas (*662*) and others, though the duration of the rising phase (2.0σ) may possibly be very slightly greater. The observed value is undoubtedly higher

than that of any constituent fibre, for as Gasser *et al* (*386*, *387*) have found in nerve, even the slightest degrees of asynchronism greatly alters the time to maximum of the action current. For our present argument it matters very little whether the duration of the true latency and the rising phase of the action current coincide or not, *the important point is that the beginning of the electrical response does invariably precede slightly the mechanical.* This being the case it is difficult to give credence to Mines' (*717*) suggestion that the electrical response is caused *by* the liberation of energy, or as he suggested more specifically by the action of lactic acid upon the contractile interfaces. It would in fact appear that it is precisely the other way around: *viz.*, that the action current has its origin in the wave of permeability which in itself leads to the formation of lactic acid. In other words, the mechanical response, which may be taken as the index of lactic acid formation, occurs after, and not before, the action current. We shall see in later chapters that this inference is also supported by the relation which exists between the size of the action current and the initial energy liberation of the muscle fibre.

SUMMARY

The latent period of shortening may be divided into four phases, which in the frog's gastrocnemius at 20°C. have the following characteristics: (1) Conduction time in the nerve. With 3 cm. average inducting distance, as in these experiments, the interval would be 1σ (30 m. per second). (2) Delay at the end-plate. An interval of 4σ was observed between the stimulus and the muscle action current. The end-plate delay was therefore 3σ. Reasons are given for regarding the so-called end-plate delay as due largely to slowing of conduction in the slender terminal branches of the motor nerve. (3) "True" latency. The interval after the beginning of the electrical response during which the mechanical conditions are unaltered. This is the same whether determined by thickening or by the response of the tendon, and has an absolute value 1.5 to 2.0σ. (4) Rigidity. When a second response falls during the relaxation from response I, the muscle ceases to relax 1.5 to 2.0σ after the action current, and becomes "rigid" for a period 4 to 5σ *before shortening.* This accounts for the supposed difference between the latent period as determined by thickening and by shortening of the tendon. The influence of temperature upon the phases of the latent period is described.

CHAPTER III

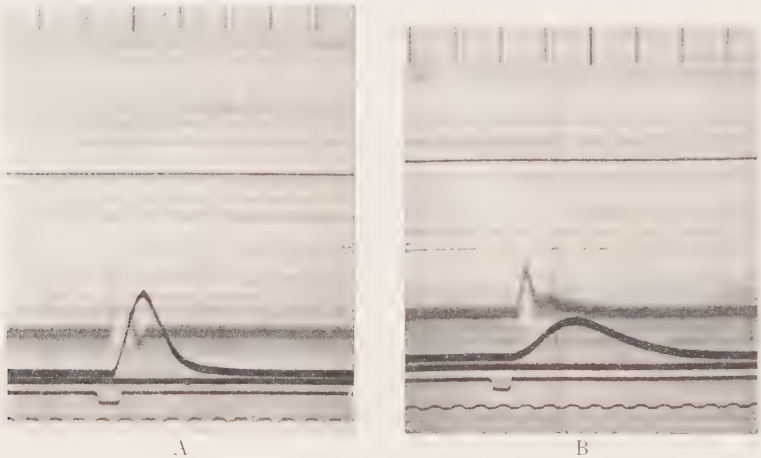
The Nature and Course of the Isometric Twitch

In one important respect reflex responses of muscles and of muscle groups differ from the responses produced by artificial stimulation of a motor nerve. When elicited by an induction shock, motor nerve impulses are set up with approximate simultaneity in all fibres excited; in reflex responses, on the other hand, no matter how they are called forth, large volleys of impulses are probably never completely in phase. Even in a reflex flexor "twitch" (Forbes and Gregg, *320*) elicited faradically, or in a knee-jerk (Chapter XI), the volley of centrifugal impulses is considerably spread out in time, the first impulse of the volley reaching the muscle several sigmata before the last. When a volley of motor impulses is somewhat asynchronous it is impossible to infer from the characteristics of the contraction of the whole muscle the nature of the response of each constituent fibre. To study fibre responses, therefore, it is necessary to prove that all fibres in a muscle mass begin and cease contracting simultaneously, or approximately so, for only under these circumstances can a maximal contraction of a muscle be regarded as an accurate index of the response of separate fibres.

Synchronization of Contractile Elements (*359*)

To obtain approximately synchronous responses it is necessary: (1) That the muscle be fresh and intact with active circulation, and that the preparation respire freely through its lungs and (frog) moist skin; (2) that the recording muscle be fixed with absolute security, as the slightest "give" on the part of the muscle or of any of the recording instruments may greatly distort the characteristics of the response; (3) that the muscle pull in its accustomed direction; (4) that the muscle be initially under relatively high tension so that a minimum of time may be lost in conducting the tension wave through inactive parts of the tissue; (5) that the conducting distance in the nerve be as short as is practicable; (6) that the muscle be as nearly as possible parallel-fibred, for when the individual fibres are diagonally arranged in a muscle, some fibres shorten more than others, and as shortening alters the duration of the mechanical response, all of the fibres will not cease contracting at the same time. When the gastrocnemius muscle is used this source of error may be minimized by arranging that the muscle shall be initially stretched and the response of the whole muscle be as nearly as possible isometric—but even these precautions do not completely prevent slightly varied degrees of shortening among the individual diagonally arranged fibres (*361*). Further discussion of the problem of syn-

chronization will be found elsewhere (*359*). It may be noted in passing, however, that when stimulated through the nerve the most distal fibres of gastrocnemius (20°) respond not later than 1σ after the most proximal fibres. This has been demonstrated by galvanometer records. In the case of the sartorius muscle, on the other hand, (frog) it is virtually impossible to obtain a response in which all fibres act as a unit throughout their entire length, for electrical records show that the pelvic (non-neural) end, even when intact and stimulated through its nerve, responds several (2 to 3σ) sigmata later than the neural region (18°). When the excised sartorius (which violates number 1 of the six conditions mentioned above) is stimulated directly at its pelvic end,—the proximal galvanometer lead being taken from the mid-region of the muscle,—the mechanical response begins, as



A B

FIG. 33. Showing two responses of a sartorius muscle, one intact (A), with active circulation, the other (B) excised and stimulated directly by a just maximal shock at its pelvic end. $T = 16.0°$. Galvanometer leads taken from tendon and belly of muscle. In B the mechanical response has commenced several sigmata *before* the electrical, as a result of the contraction not being synchronous throughout the length of the muscle. Frequency of myograph 430 per second. Time above 0.04 second.

shown in figure 33 B, before the excitatory wave has reached the proximal electrode This illustrates a disadvantage of using excised muscle for such experiments, as well as the danger of not leading from the point stimulated.

THE SHAPE OF THE ISOMETRIC TWITCH RECORD[1]

Much has been written concerning isometric contraction of skeletal muscle, but a review of the extensive literature concerning this phase of

[1] This section has been expanded from a paper recently published in the *Proceedings of The Royal Society of London* (*354*).

muscular activity is beyond the scope of the present monograph.[2] Investigators before Sherrington (1921) had been unable to record the isometric twitch with sufficient accuracy to demonstrate certain important features concerning its shape. This was due largely to imperfections in the mechanical recording apparatus and also to the fact that many investigators employed excised rather than intact muscle. Sherrington (*932*) demonstrated by means of his torsion-wire myograph (see Appendix) that the record of the twitch of the intact tibialis anticus of a cat regularly exhibits a flat top, which terminates more abruptly than it begins, and Liddell and Sherrington (*637*) confirmed this for the semitendinosus and quadriceps extensor of the cat. Responses of tibialis anticus obtained by

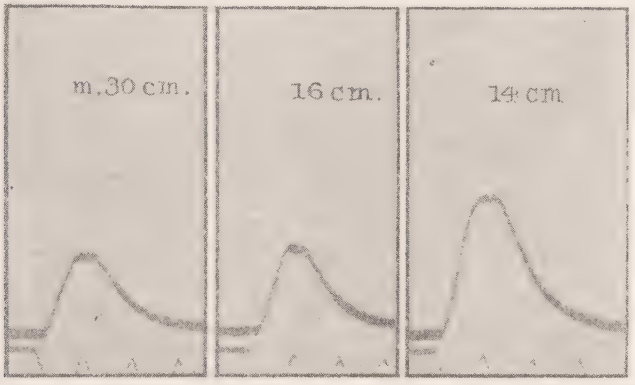


FIG. 34. Responses of tibialis anticus of a cat to direct stimulation of the motor nerve. Intensity of stimulation indicated in each figure. From Sherrington's communication in which the torsion-wire myograph was first used (*Proc. Roy. Soc.*, vol. 92B, p. 252).

Sherrington are reproduced in figure 34. The abrupt termination of the plateau to which he directs attention is an important feature of the twitch record, as is also the existence of a plateau. Another feature which their figures show is the abrupt commencement of the increased tension (fig. 34). The ascent was usually sudden and convex (upward) in outline exhibiting little if any of the S-shape so often figured in isometric twitches, in fact the point of inflection from concavity to convexity in the majority of their records is usually so low as to be immeasurable. These three

[2] A summary of the early literature will be found in Burdon Sanderson's chapter in Sharpey-Schafer's *Textbook* (*181*), and more recent work is discussed in Nagel's (*342*) *Handbuch*. The most recent work is summarized (1925) in Fenn's chapters in Bethe's *Handbuch* (*300, 301*).

features, therefore,—(1) the abrupt and convex ascent, (2) the plateau, (3) the sudden termination of the plateau, may be taken as fundamental characteristics of a single isometric contraction curve of intact muscle. The investigations about to be described confirm Sherrington's observations and in certain points amplify them. They were performed under his supervision with a myograph of his design chiefly upon decerebrate frogs, but the gastrocnemius and rectus femoris of spinal and decerebrate cats were also used.

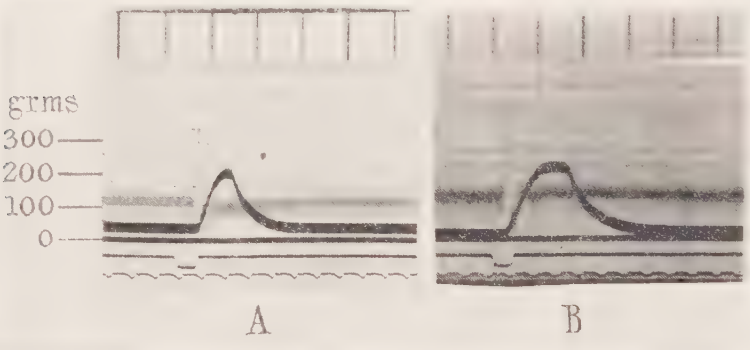


FIG. 35. A. Twitch of the intact gastrocnemius muscle of a 30 gram frog at 24.5°. Time is shown above in 0.04 second; and below in order (from above downwards) are the shadows of the galvanometer string; the myograph; the line of zero tension; the short circuiting key connected with stimulating electrodes (open for 0.02 second); and the "wiggler" showing the frequency—50 per second—of the torsion wire separation key. (This somewhat involved method of stimulating was used in order that the twitch might be followed when desired by a short tetanus of break shocks). The initial tension is 35 grams and the tension developed above initial is 165 grams. The duration from the electrical response to the "angle" is 33σ. Tension of string 6.5 mm. per millivolt; magnification, 285.

B. Twitch of the same preparation at 16°. Initial tension 15 grams; tension developed above initial 140 grams. The duration to the "angle" is 53σ. Tension of string: 42 mm. per ampere. Other conditions as in A (*354*).

THE "ANGLE" AND THE CONDITIONS NECESSARY FOR OBSERVING IT

In addition to the flat top, which is a noticeable feature of the twitch record of an intact frog's gastrocnemius as well as of the muscles of the cat, a striking character of the twitch in the frog is the abrupt termination of the plateau (see fig. 28 B, Chapter II, and fig. 35 A and B). The transition from the plateau tension to subsiding tension is abrupt enough to form on the linear record a clearly defined angle. In a fresh preparation

with active circulation, so precise is this angle that it may be used as an exact and convenient point from which to measure the mechanical duration of the twitch. When the electrical changes are recorded, as in these experiments, simultaneously with the mechanical response, one may take as the most accurate interval for measurement of twitch duration the period from the beginning of the electrical change to the angle at the end of the crest of the twitch record. The corner thus defined may be appropriately termed the "subsidence angle," and in the remainder of this work it will be referred to simply as the "angle." With the method of recording described in the Appendix, both points may be measured significantly to 0.001 second (1σ).

For observation of the "angle" in the isometrically recorded twitch, certain conditions are necessary. (1) A recording lever of high natural vibration frequency is an essential, for even a myograph having a rate of 460 per second tends, as shown in figure 35 A, slightly to obscure the "angle" of a muscle twitch at 24.5°. (2) A second condition, already explained, is absolute immobility of the fixed attachments of the muscle, since the slightest "give" of tendon, knee-joint, or moist chamber modifies the "angle." (3) The precautions mentioned above for securing perfect synchronization of the contractile elements are also necessary for its observation. (4) A mechanical precaution not previously emphasized is the reduction to a minimum of inactive constituents and of frictional resistances within and surrounding the muscle. Following the "angles" of mammalian responses, especially when submaximal, one often observes a very slight initial convexity. It was found (*365*, p. 579), however, that if the rectus muscle of a decerebrate cat is freed from its fellow muscles in quadriceps and freed as well from all fascia, skin and other frictional resistances about the tendon, a maximal twitch then showed an "angle" as precise as, it not more precise, than the "angle" observed in the frog. This observation is of importance since in mammals the rectus is a parallel-fibred muscle. It indicates that the "angle" represents a discontinuity in the response of the individual fibre, and removes any remote possibility of its being associated in the gastrocnemius with the diagonal disposition of the fibres.

If only a portion of the fibres in gastrocnemius is made to respond, as when stimulating through one of the lumbar roots (see Chapter VI), the "angle" is generally less sharp than when both lumbar roots are stimulated together. This also is probably to be attributed to the frictional effect of inactive constituents (*358*).

In addition to the mechanical factors just mentioned, two purely physio-

logical factors influence the "angle." (5) One is temperature. As might be anticipated, the "angle" is sharper at high temperatures than at low (cf. figs. 28, 35 A and B). (6) But of greater importance than any factor so far mentioned is the fresh and uninjured condition of the preparation. The better the condition of the preparation especially with reference to blood-pressure, circulation, and respiration, the more precise is the "angle."

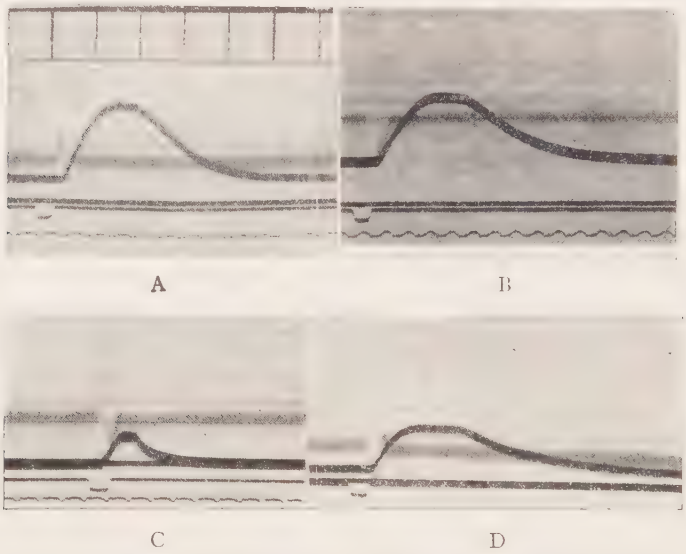


FIG. 36. A. Twitch of an excised gastrocnemius preparation at 16°; the "angle" obscured. Initial tension, 70 grams; tension developed, 230 grams, duration 65σ. Tension scale, time and other conditions as in fig. 35.

B. Twitch of spinal preparation (no respiration) at 15°. Initial tension 120 grams; tension developed, 180 grams.

C. Twitch of normal muscle when slack, 2 mm. shortening occurring before becoming taut. 24°. String at 45 mm. per ampere.

D. "Abnormal" twitch of normal muscle after prolonged rest; same preparation as in figure 38 at 17.0°; string 40 mm. per ampere. Initial tension 40 grams, tension developed 140.

An excised gastrocnemius muscle, no matter how carefully it may be bathed in accurately buffered Ringer's solution, shows an obscured "angle" after several responses (fig. 36 A), and an intact muscle whose circulation has been stopped for 20 to 40 minutes behaves like an excised muscle. Also a preparation which may have a more or less active circulation but in which the respiration has stopped (usually owing to decerebrating too

low) soon shows in the response of its muscles a delayed relaxation which dulls the "angle," though it may not necessarily obscure it completely (fig. 36 B). And, lastly, excessive stimulation obscures the "angle" of a muscle even when the circulation is active. This does not necessarily indicate, however, that the "angle" of each constituent fibre has become modified, for, as we shall see in Chapter V, disappearance of the "angle" with fatigue is probably due to asynchronous cessation of fibre activity. Recent observations of F. H. Pratt (unpublished) have shown that curve of contraction of isolated fibres, as recorded by the mercury droplet method (see Introduction), possesses the same features as have been described herein for the twitch curve of the whole muscle. The "angle," moreover, apparently does *not* disappear when the individual fibre response shows evidence of fatigue.

I have recently found that when a muscle is quickly excised the responses, if taken immediately, may show distinct "angles," *provided the muscle is not put in Ringer's Solution.* When put into accurately compounded "Ringer,"[3] the responses within two or three minutes become greatly prolonged (30 to 50 per cent) and the "angle" may become unrecognizable. In one experiment in which 1 per cent gum arabic was added to the "Ringer" the onset of these changes was slower, but the point requires further investigation. An excised muscle will show its "angles" for an hour if kept (unstimulated) in purified liquid paraffine at a low temperature (8 to 10°).

In connection with fatigue, it seems worth while to record that occasionally, especially in winter frogs in which the condition is probably bad, preparations are met with in which, even though the circulation is active, the "angle" of the twitch is from the start almost completely obscured. Frogs which have been confined for several months almost invariably show a somewhat modified relaxation. To ensure normality of response, with precise angles, freshly caught "summer" frogs are to be recommended. It would appear from this that the "angle" provides an index of the condition of the animal as a whole, quite apart from fatigue. Temporal dispersion of fibre activity, due probably to differing physiological states of the separate fibres, suggests itself as the most likely cause of the modified "angle" in winter frogs.

[3] Owing to the fact that many authors have not stated the nature of their Ringer's Solution much uncertainty has arisen in the literature. The solution used in the present work was composed of:

NaCl	0.65	$NaHCO_3$	0.02
KCl	0.014	NaH_2PO_4	0.001
$CaCl_2$	0.012	Water	to 100

made up in distilled water. It was used both with and without phosphate, but this did not materially affect the results obtained.

It is clear from what has just been said that the more perfect the mechanical and physiological conditions of recordings are made, and the better the condition of the preparation itself, the more precise is the "angle" at the end of the twitch plateau.

OTHER FEATURES OF THE ISOMETRIC TWITCH

The "angle" of sartorius. The difficulties of fixation, as noted above, have rendered it impossible to obtain an accurate record of the twitch of the intact sartorius. Some records, however, show a trace of an "angle." Through the courtesy of Dr. Adrian, I have been permitted to reproduce in figure 37 an isometric response showing a distinct "angle" which he obtained from a freshly excised sartorius preparation, (see Adrian, *8*). Hartree and Hill (*440*) have also described a feature of the responses of

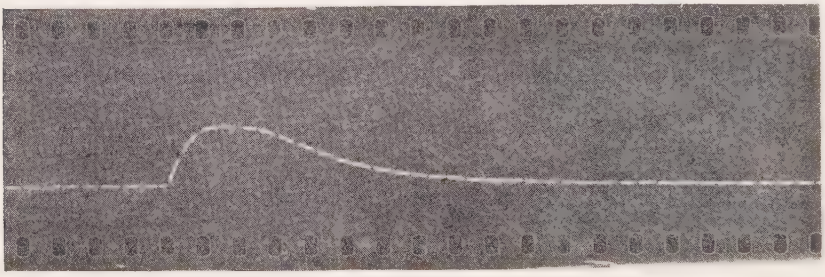


FIG. 37. A record of the response of a freshly excised sartorius muscle showing an angle. This was obtained three years ago by Dr. Adrian who has very kindly permitted me to reproduce it.

the excised sartorius which undoubtedly owes its existence to the "angle." They observed in a number of their isometric twitches a more or less sudden turn of the myograph which they designated the "hump." They observed it more often at low temperatures than at high, and were convinced that when it occurred it was "physiological" in origin. They were unable, however, to decide why it occurred in some responses and not in others, and they suggested (*440*, p. 399) that it might perhaps be due "to the superimposed contractions of two separate elements in the muscle or the muscle fibre." The progressive modification of the mechanical response which occurs when an excised muscle is placed in "Ringer" (see above) undoubtedly accounts in part at least for the variability of Hartree and Hill's records, for the progressive changes of the muscle in Ringer's solution proceed much more rapidly at high temperatures than at low and would therefore

obliterate the "angle" more quickly at higher temperatures. It is evident from these observations that the response of a fresh sartorius when properly fixated and adequately stimulated is also characterized by an "angle," similar to that of gastrocnemius.

The "staircase" effect, etc. A further point of interest is that the twitch of a normal muscle which has been for an hour or more at rest is "abnormal," in that it develops less tension than usual, but persists for a greater length of time than an ordinary twitch (fig. 36 D and fig. 97, Chapter IX). After several responses it becomes quite "normal" (as in figs. 35A and B); this may, therefore, be regarded as a manifestation of the "staircase" effect. Pratt (*781, 782*) has observed this effect in the responses of single muscle fibres. Further observations on the staircase effect will be found in the next chapter.

A muscle stimulated *directly* never shows as sharp an "angle" as a muscle stimulated through its nerve, unless the direct stimulus be so strong that the cathode spreads over the entire muscle (cf. Kato, *541*, Adrian, *8*, Bethe und Happel, *97*). This is probably caused by the lower rate of conduction in muscle than in nerve, the contraction of the individual fibres becoming somewhat out of phase, while with indirect stimulation they respond more nearly simultaneously.

When properly recorded, the ascent of the isometric twitch record of intact muscle (sartorius or gastrocnemius) never appears S-shaped, but always commences abruptly and is convex (upward) in outline. By ascent is meant the upstroke of the curve following the period of rigidity (Chapter II). If the period of rigidity were considered, it would of course constitute an initial short concavity in the curve. The S-shaped ascent so often figured has been observed with *excised* sartorius stimulated directly at the pelvic end (fig. 33 B). This, as Adrian (*8*), and Bethe und Happel (*97*) have pointed out, causes a wave of contraction to pass along the muscle with the result that the fibres are not contracting simultaneously throughout their entire length. It is clear, therefore, that the S-shaped ascent, especially when pronounced, is an artefact and not a faithful record of the course of the response of a fibre at a given point. S-shaped ascents are also seen when the preparation is not adequately fixated.

The crest of a twitch record of a frog's gastrocnemius is most usually parallel with the base-line, *i.e.*, it is a true plateau. Occasionally, however, the crest slopes toward the base-line, and in mammalian twitches it almost invariably slopes in this way. The sloping plateau was encountered frequently in early experiments, especially when large frogs were used. When the method of fixating the muscle was improved by the use of the

upright described in figure 10 of the appendix, the sloping plateau was not again encountered. It is probable therefore that the slope so often seen in mammalian twitches is due either to a slight "give" on the part of the fixating device or, more probably, to gradual stretching of the anatomical attachments of the muscle. The elasticity inherent in such a long muscle as the exposed rectus of the cat often caused a slight initial concavity in the ascent of its twitch.

The influence on the "angle" of conducting distance in the nerve may also be mentioned. The slight tendency of the constituent impulses of a volley to become asynchronous, owing to small differences in the rate of conduction in different fibres, does not appear to be sufficiently great at 15° to produce a significant modification of the "angle" at conducting distances between 1 and 5 cm. In one experiment, however, at 7° the "angle" was somewhat less sharp at 5 cm. nerve conducting distance than at 2 cm. It is likely that this is to be attributed to the Erlanger-and-Gasser effect.

In view of the abrupt discontinuity in the contractile process causing the "angle," it is significant that there is no electrical counterpart of this sudden change. An examination of the string in any record of a twitch will show that it is absolutely quiet at the "angle" (figs. 35 and 38).

It is noteworthy that a muscle, when permitted to shorten several millimetres before developing appreciable tension in its tendon, exhibits, as does a stretched muscle, a flat top and precise "angle" (fig. 36 C). Hence, inasmuch as a muscle must develop a considerable degree of internal tension to overcome its own internal viscosity, it appears probable that a muscle allowed to shorten isotonically would also exhibit features in its time course comparable to the flat top and abrupt relaxation characteristic of isometric records.

Curve of relaxation. The shape of the curve of relaxation following the "angle" is a matter of some interest. In the figures of muscle responses, as ordinarily recorded, the beginning of relaxation commences with an upward convexity followed by a concave sweep which forms the larger part of the descent. It has been found that the initial slight convexity was due in large measure to the friction of skin, fascia and inactive constituents of the muscle, for when the rectus was dissected away from its surroundings, the relaxation from a maximal twitch tended to produce a curve concave throughout its entire extent. In the same way the twitch record of an unfatigued frog muscle in good condition is, in my experience, often without any initial convexity, being similarly wholly concave (fig. 28, Chapter II, fig. 38). Initial convexity ("nose") in the relaxation period

of a response is usually associated with fatigue, for it invariably is present after stopping the circulation and after prolonged stimulation, being due, as we shall see, to asynchronous cessation of activity. In a muscle with diagonal fibres, even when fresh, a "nose" may be present, which is due also to asynchronous cessation of contraction of the individual elements, for the "nose" is more pronounced the more the muscle shortens. It is pointed out below that when a muscle is allowed to shorten during the response, the *duration* of the response is less than in a perfectly isometric contraction. When the extent of the shortening is unequal among the individual fibres of a muscle (as is inevitably the case when a diagonally-fibred muscle shortens), the duration of response of individual fibres will not be the same, *i.e.*, cessation of contraction will be asynchronous, and the "angle" due to the responses of the individual fibre will be fused into the rounded "angle" of the whole response.

Discussion. We have now described at some length the factors which affect the so-called "angle" of the isometric twitch record of skeletal muscle, and though further information concerning the nature of this discontinuity will be presented in the following sections on summation and the effect of temperature, certain points are already clear. One may safely infer that the "angle" characterizes the myogram of each individual fibre, and is therefore a feature of fundamental importance in muscle physiology. Pratt, as I have already mentioned, has observed the "angle" in the response of an individual fibre. It is evident, however, that in the normal responses of muscle while in the body, every condition militates against the appearance of "angles," and the great wonder is not that the "angle" becomes so easily smothered but that it is ever so sharp as it sometimes is (fig. 38). In the complex assemblage of units in a diagonally-fibred muscle it is indeed surprising that the activity of each fibre is so perfectly adjusted mechanically that when all fibres are simultaneously stimulated, the muscle as a whole behaves so *nearly* as a unit, reflecting the response of each constituent. Elasticity of active and inactive constituents, asynchronism in the commencement of the response, and inequalities in the duration of the response of each individual fibre all combine to modify the "angle," and each of these modifying factors becomes increasingly effective when the muscle is removed from the body. From the viewpoint of animal economy, it is of course fortunate that the asynchronous nature of reflex and voluntary responses (Chapter XIX) causes a complete obliteration of the "angle"; otherwise the abrupt onset and cessation of contraction would make orderly locomotion impossible.

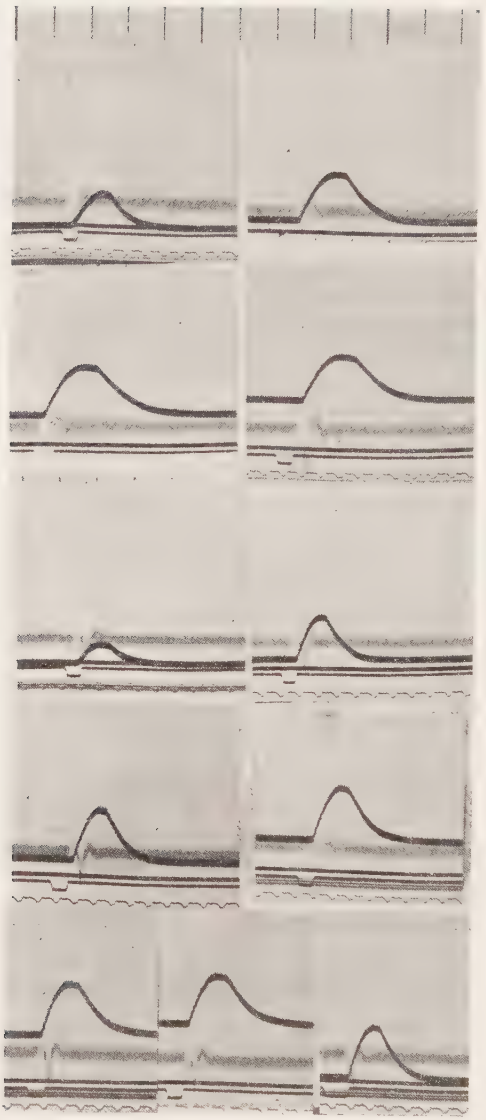


FIG. 38. (A to D.) Series of twitches of the intact gastrocnemius of 30 gram frog at 19° under increasing initial stretches. 2.2 cm. = 500 grams. String tension: 55 mm. per ampere. Time above 0.04 second. In these records the shadow of the string has been somewhat retouched, which accounts for the slight irregularities. (E to K.) Series of twitches from same preparation at 23.5°. String at start 55 mm. per amperes; at finish 50 mm. per ampere. (In a prolonged experiment, owing to the heat of the arc, the string tends to become slightly tighter; the electrical responses are in consequence somewhat smaller relatively at the end than at the start.) The measurements of this series are given in table 4.

THE EFFECT OF INITIAL TENSION ON THE DURATION OF THE TWITCH

Having established the "angle" as of normal occurrence in the response of intact muscle, it became a problem of some interest to investigate the old question of the effect upon the duration of the twitch of increasing initial tension. Lucas (*658*) early showed that for excised muscle the duration of the arrested isotonic twitch is enhanced by increasing the tension, and Hartree and Hill (*440*), as well as many others, have confirmed this general result. Since the "angle" represents a fundamental discon-

TABLE 4

Showing the effect of initial tension upon the magnitude of the mechanical and electrical responses of the isometric twitch (intact gastrocnemius, 30-gram frog; photographs of experiment shown in figure 38)

FIG. 38	INITIAL TENSION	TENSION OF PLATEAU	TENSION ABOVE INITIAL	DURATION TO "ANGLE"	DURATION FROM "ANGLE" TO HALF-RELAXATION	SIZE OF ELECTRIC RESPONSE*
			At 19°C.			
	grams			*0.001 second*		*mm.*
A	5	118	113	49	12	21.5
B	45	218	173	57	19	23.0
C	110	291	181	63	21	24.5
D	175	345	170	64	20	24.0
			Same preparation at 23.5°C.			
E	5?	113?	108	39	10	17.0
F	34	183	149	40	13	18.5
G	57	243	187	42	16	19.0
H	110	308	198	44	17	20.0
I	172	358	186	46	16	20.5
J	218	396	178	48	16	20.0
K	25†	190	165	40	14	16.0

* Electrical responses *not* corrected for tightening of string during experiment.

† Control observation taken at the end of the experiment.

tinuity in the course of the response, one may ask whether the intervals before and after the "angle" are both enhanced by tension. For convenience the interval between the beginning of the electrical response and the "angle" may be termed the "E-A interval" (as distinguished from the "E-M interval:" *i.e.*, the interval between the beginning of the electrical response and the beginning of shortening).

The prolongation of the "E-A interval," which accompanies increasing initial stretches was found much less than might have been anticipated

from the results obtained with surviving muscle, being in one experiment only 10σ for a range of 0 to 218 grams initial stretch. A more noticeable result of increased initial stretch is the increased active tension developed in the twitch (see fig. 38, and table 4). Thus, in one experiment at 34 grams initial stretch the plateau was reached at 183 grams, 149 grams being developed above the initial; the same muscle at 110 grams initial tension reached its plateau at 308 grams, thus developing 198 grams above its initial stretch. As to the electrical response, its magnitude varies (but not directly) with the tension developed (see table): when, for example, 60 grams are developed above the initial stretch, the excursion of the string is somewhat less than when 115 grams or more are developed.

The phase of relaxation of the twitch may be examined by measuring

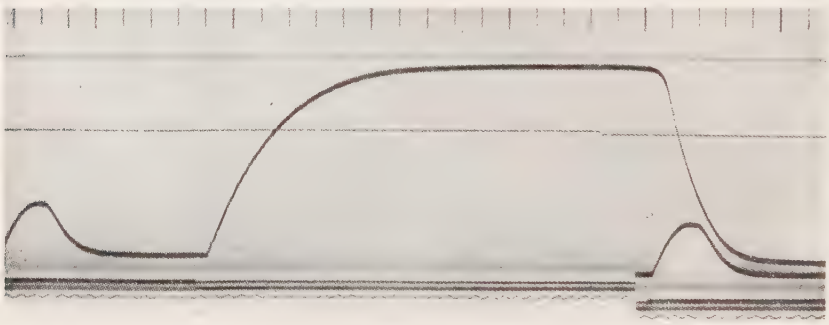


FIG. 39. Twitch followed by a short tetanus in which the twitch has been placed immediately beneath the corresponding part of the curve of relaxation of tetanic response to show the similarity between the two curves. $T = 15°$.

the interval between the "angle" and the point of half-relaxation. For convenience this interval will be referred to as the "A-$\frac{1}{2}$R interval." Increase of the initial tension increases this interval in an ensuing response. Unlike the "E-A interval," however, the "A-$\frac{1}{2}$R interval" passes through a maximum with the tension developed (above initial). This is shown in table 4. If the duration of the "A-$\frac{1}{2}$R interval" in the twitch is divided by tension developed above the initial, a value is obtained in an unfatigued muscle which is nearly constant at all initial tensions (cf. table 9, Chapter IX). This has been taken to indicate that the "*rate* of proportional fall" of tension is constant (*440*), a fact which supports the inference that relaxation is a passive process, and that the concave nature of the curve results from the internal frictional and viscous forces within the muscle. A further point in favour of this inference is the fact, illustrated in fig-

ure 39, that the shape of the relaxation curve of a twitch almost coincides with the shape of the corresponding position of the curve of relaxation from a tetanus. In this figure the twitch has been moved under the tetanus.

INFLUENCE OF SHORTENING DURING THE TWITCH (*361*)

The effect of varying the degree of shortening occurring during a twitch has been investigated by recording responses in which the muscle was

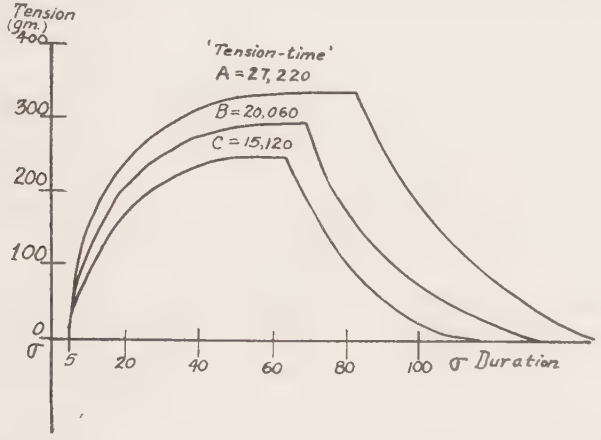


FIG. 40. Twitches of an intact frog's gastrocnemius muscle at 15° in which varying degrees of shortening occurred during the responses, plotted on the same tension-time coördinates. The product of the tension × the time (gram × σ) is indicated above each curve. The initial tension was constant (50 grams) in each response. Stimulus a maximal break shock applied to sciatic nerve.

	Shortening mm.	*Tension developed gm.*	*Duration to Angle 0.001 second*
A	0.025	332	82
B	0.21	295	68
C	0.41	244	63

attached to the myograph—the initial tension being constant—at various points along the horizontal arm projecting from the central axis of the instrument. This horizontal lever arm may be seen in figures 1 B and 2 of the appendix. The extent of the shortening in any given response can be calculated from the known constants of the myograph and the optical system.

In ten experiments in which the shortening allowed during the twitch has been varied, it was found that *the smaller the shortening permitted the*

greater the tension developed and the longer the duration of the response measured to the "angle." In figure 40 three responses of the same preparation taken at short intervals are plotted on the same tension-time coördinates. It will be seen that as between a twitch with 0.02 mm. tendon shortening and one in which 0.52 mm. occurred there is a difference of more than 25 per cent in the tension developed and a similar difference in the duration of the respective twitches. This, in other words, amounts to a diminution of nearly 50 per cent in the total area ("tension-time") of the response. In some experiments even greater differences have been noted, in others it has been somewhat less. Whatever the explanation of this phenomenon may be (see Chapter VIII), it is clear that contractile energy, *i.e.*, the power of developing tension, is lost as a result of shortening. The "angle" in these responses is also affected by the extent of shortening permitted, being somewhat sharper in responses with the least shortening.

TABLE 5

Showing the effect of varying degrees of shortening occurring during the twitch of gasirocnemius (frog)

EXPERIMENT	APPROXIMATE SHORTENING OF THE MUSCLE					
	0.02 mm.		0.10 mm.		0.52 mm.	
	Tension developed	Duration	Tension developed	Duration	Tension developed	Duration
	grams	*0.001 second*	*grams*	*0.001 second*	*grams*	*0.001 second*
10, iv, 25 (18°)	332	82	295	68	244	63
25, iii, 25 (11°)	275	160	260	125	245	117
11, iv, 25 (16°)	360	80	270	69	222	61
28, iii, 25 (15°)	400	90	310	71	250	64

Since in these experiments the electrical responses are of constant size so long as the initial tension remains the same, it would appear—in view of the enhanced duration of the twitch when the tendon shortening is small—that a given quantity of energy liberated by a stimulus is dissipated most slowly when the muscle cannot change its shape. This will be referred to again in Chapters VIII and IX.

This recalls the old controversy between Schenk and Blix (see Lucas, *658;* and Biedermann, *103*, vol. 1, p. 78), as to whether an arrested isotonic contraction relaxed sooner or later than a normal contraction. Lucas showed by an optical method that the controversy turned upon the ratio of the moment of inertia of the recording lever to the mass at unit distance from its axis, and that when this ratio is made as small as possible the

arrested isotonic contraction *is* of greater duration than the normal twitch. This is clearly in keeping with the greater duration of the twitch which we have just observed as the degree of freedom for shortening is diminished.

THE INFLUENCE OF TEMPERATURE ON THE TWITCH

The foregoing considerations indicate that the "angle" represents a discontinuity in the course of the response in each individual fibre. It is therefore of interest to examine the effect of temperature on the phases of the twitch preceding and following this discontinuity. Experiment has shown that the interval between the beginning of the action current and the "angle" is approximately halved by raising the temperature from 10° to 20°. In other words, the Q_{10} of this "E-A interval," which in the present

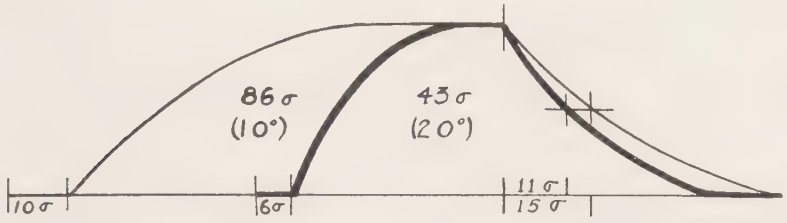


FIG. 41. Two twitches from an intact gastrocnemius of a decerebrate frog at 10 and 20° respectively, plotted on the same coördinates so that their respective "angles" fall at the same point. Equal tensions were developed so that the only variable component of their respective phases is duration. It will be seen that the duration of the interval between the electrical response and the "angle" falls from 86 to 43σ with a rise of 10° ($Q_{10} = 2.0$), while the duration of relaxation falls only from 15 to 11σ ($Q_{10} = 1.36$). The total interval between the action current and the beginning of shortening is diminished from 10 to 6σ by a rise of 10°.

monograph is referred to as the "duration of the twitch," is approximately 2.00 (fig. 41). In making such determinations it is of course essential to average large numbers of observations from the same preparation, also, to guard against deterioration, it is important to secure control observations at the original temperature at the end of the experiment. In table 6 are summarized the values obtained from two typical experiments. In the first experiment on returning to 12° the average duration of the twitch had a value of 122σ, which provides ample evidence that the preparation did not deteriorate excessively in the course of the experiment. Further details are given in the original description (*363*).

If the rate of relaxation of the twitch is examined, one finds that the process is but slightly affected by temperature alterations. This is shown diagrammatically in figure 41. It will be seen that the time required at

20° for the muscle to reach half-relaxation is 11σ while that required at 10° to reach the same point is 15σ, this yields, for this particular temperature interval, a Q_{10} lying between 1.3 and 1.4. The experimental record from which this figure has been plotted is shown in figure 63. It will be seen that a value of 1.36 contrasts strikingly with the Q_{10} for the duration of the twitch (2.0). This suggests that the respective phases of the twitch are the expression of fundamentally different processes. Had the Q_{10}'s been the same it might have been assumed that the mechanical shape of the whole twitch merely reflected an internal process such as a rising and falling of the concentration of activating ions, the increasing concentration

TABLE 6

Showing the Q_{10} for the duration of the twitch. Frog's gastrocnemius. Measurements in σ. Initial tension in both 100 grams

EXPERIMENT (22.X.24)		EXPERIMENT (24.X.24)	
12°	22°	13°	23°
121	57	113	50
120		111	51
119	59	112	53
121	58	116	54
118	60	115	53
119	61	116	52
124	59	112	53
121	61	118	53
122	60	117	54
Sum.....1,085	475	1,030	473
Average.....120.5	59.4	113	52.5
$Q_{10} = 2.02$		$Q_{10} = 2.12$	

causing the *ascent* of the twitch and the falling concentration producing the curve of relaxation. In this case the two processes would presumably be affected equally by temperature alterations, but this is not the case. This result is accordingly in keeping with the conclusion reached on other grounds that the curve of relaxation is the expression of an essentially passive process, such, for example, as the sudden stretching (in this case by the myograph lever) of a viscous elastic body.

The early investigations on the influence of temperature upon various phases of muscular activity were summarized in 1907 and 1908 by C. D. Snyder (*950, 951*), and in a series of notable contributions (*951, 953, 954, 958*) this author helped to lay the foundation of present-

day physiological interpretation of temperature effects. He pointed out that the duration of the "shortening phase of skeletal muscle action" was approximately halved by a rise of 10°, the Q_{10} varying from 2.0 to 2.5. From the data of Yeo and Cash (1064), Snyder calculated the critical thermal increment, μ, for this phase of activity and found it to be about 12,000. It is evident that these values correspond closely with those obtained in the present research for the "duration of the twitch." Snyder also suggested that on *a priori* grounds one would anticipate a low value for the rate of relaxation of a twitch, since this is most likely a passive process, governed possibly by the viscous properties of the muscle. The Q_{10} of the viscosity of cat's and hog's blood serum was found by Snyder and Todd (*958*) to be of the order of 1.3, a value close to that obtained recently (1924) by Pantin (*749*) for the viscosity of the protoplasm of unripe *nereis* eggs ($Q_{10} = 1.4$). Snyder, however, was unable to find experimental values for the rate of relaxation having a Q_{10} less than 1.9 for any type of muscle (with the exception of the somewhat special case of the cat's bladder from which a value of 1.3 was obtained by C. C. Stewart), and this led him to question the viscosity hypothesis as applied to relaxation. "The data (Fick) now at hand," he says, "are sufficient to show that this phase of muscle action cannot be passive" (*951*, p. 318). As already indicated, the new technique of the torsion-wire myograph and the recognition of the "angle" as the point of commencement of relaxation have made possible a revival of this discarded theory. When "pure" (*i.e.*, when unmodified by temporal dispersion of activity among individual fibres), the curve of relaxation has a Q_{10} of 1.3 or thereabouts, which is clearly in keeping with the viscous hypothesis (see also Chapter V).

In 1915 Kanitz (*536*) published a useful monograph entitled "Temperatur und Lebensvorgänge" to which the reader is referred for a further account of the literature relating to the interpretation of temperature coefficients. The new and suggestive conceptions recently introduced by the work of W. J. Crozier (*213–217*) cannot be considered here, but for those interested, his experimental results are particularly to be recommended since he has insisted upon the value of large numbers of observations upon organisms (or processes) in their normal physiological habitat.

The determination of a temperature coefficient for a restricted interval such as that of 10° to 20° is inadequate for mathematical treatment or for indicating the essential nature of the underlying reaction. To utilize the well-known Arrhenius formula it is necessary to obtain a large series of observations at short intervals. This was done by placing a decerebrate preparation (frog) into a large Dewar flask and recording twitches over a temperature range from 0 to 24° in intervals of 4° (363). The critical thermal increment, μ, may then be calculated from the Arrhenius formula, which is most conveniently used in the following form:

$$\text{Log}_e \frac{K_2}{K_1} = \frac{\mu}{2}\left(\frac{1}{T_1} - \frac{1}{T_2}\right)$$

where K_1 and K_2 are the twitch durations, and T_1 and T_2, the respective absolute temperatures. The values obtained in a typical experiment

are indicated in table 7, and the graphic record of the results obtained are shown in figure 42.

When the logarithm of the velocity (*i.e.*, the reciprocal of the duration of the twitch) is plotted against the reciprocal of the absolute temperature, as is necessary for adequate graphic representation of temperature effects, it is found that μ, the critical thermal increment, is approximately constant over a temperature range from 8° to 24°. In other words, the points when plotted fall approximately in a straight line, or, expressed more accurately, when large numbers of observations are plotted they fall on a narrow band

TABLE 7

The duration of the twitch of the intact gastrocnemius of a decerebrated frog contrasted at various temperatures with the duration of the interval from the "angle" to half-relaxation

Six responses were recorded at each temperature, each value in the table thus representing an average; optical isometric technique; preparation in Dewar flask, partially surrounded by gum arabic (1 per cent) Ringer solution.

TEMPERATURE	TWITCH DURATION	$\log_{10}$ VELOCITY $\times$ 1000¶	DURATION FROM "ANGLE" TO HALF RELAXATION	$\log_{10}$ RECIPROCAL "A-½R" INTERVAL $\times$ 1000
	0.001 second		*0.001 second*	
0	250	0.602	46	0.336
4	170	0.769	31	0.508
8	115	0.939	26	0.585
[10]*	[99]	[1.004]	[24]	[0.620]
12	82	1.086	22	0.658
[14]	[73.5]	[1.133]	[20.5]	[0.688]
16	65	1.184	19	0.721
20	47	1.324	16.5	0.782
24	35	1.454	(14.5)†	0.838

* Figures in brackets interpolated.

† From another experiment.

¶ The velocity being the reciprocal of the duration.

of constant slope. It has been found that the more nearly perfect the physiological conditions of experiment are maintained, as judged by the sharpness of the "angle," the more nearly rectilinear is this relation. Below 8° the points fall away somewhat from the previously established slope, but this is not invariably true and it is possible that with further improvement in the technique for maintaining more normal conditions in the recording muscle the points between 0 and 8° may also fall upon the same slope. The curve, however, becomes irregular as soon as unmodified Ringer solution comes into contact with the recording muscle (*363*).

The absolute value of the critical thermal increment for this stage of the

twitch approaches 12,000. In the experiment plotted in figure 42 the observed value was 11,950. Dr. Crozier has very kindly informed me that 12,000 is the increment commonly observed in anaerobic respiratory processes, such as that of yeast. It is therefore suggestive that the known anaerobic process concerned in initial liberation of energy should have a μ of the same value. The Q_{10} of the twitch duration for 0° to 10° is, as indicated in the table, 2.52, and for 10° to 20° is 2.10. Further consideration of the interpretation of temperature coefficients of muscular activity will be found in the communication in which these results were described.

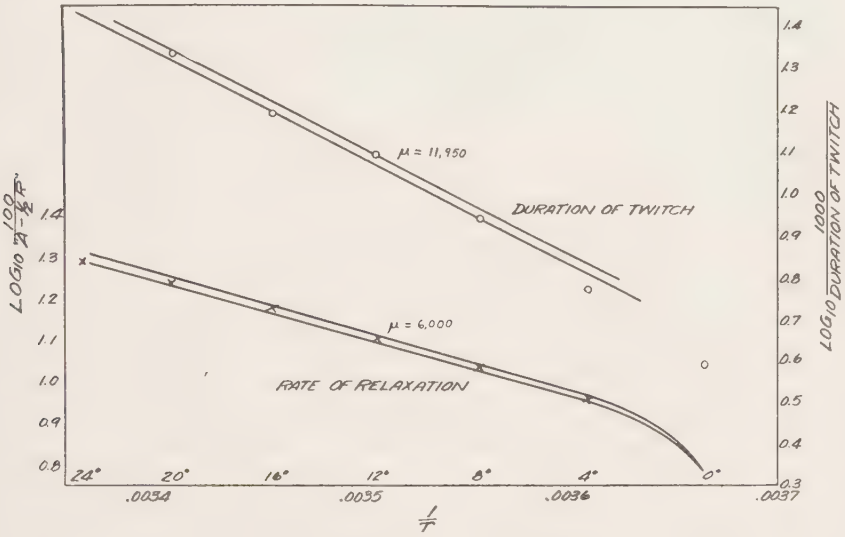


FIG. 42. A comparison of the logarithm of the reciprocal of the twitch duration ("kinetic" phase) with that of the speed of relaxation (plotted against the reciprocal of the absolute temperature). It will be seen that the slope for the kinetic phase of the twitch is greater than that of relaxation. See description in the text.

Examination of the rate of relaxation, *i.e.*, the interval between the "angle" and half-relaxation, at various temperatures, has shown that μ is invariably much lower than in the case of the twitch duration, being of the order of 5,000 to 6,000. Between 4° and 24°, moreover, the logarithm of the *rate* of relaxation (*i.e.*, the reciprocal of the "A-$\frac{1}{2}$R interval") is proportional to the absolute temperature. This is also shown in figure 42. Below 4° the rate of relaxation diminishes rapidly and the points do not fall on the slope. This observation further substantiates our original suggestion that the kinetic phase of the twitch and the phase of relaxation

are two fundamentally distinct processes. Parallel observations on the effect of temperature on tetanic responses will be found in Chapter V.

The Q_{10} of the rate of relaxation as calculated from the table is for 4° to 14°, 1.51, and for 14° to 24° is 1.38. In other experiments the values have been somewhat lower.

SUMMARY

The isometric twitch record of intact muscle, when obtained with an optical lever of high natural vibration frequency, begins abruptly and the ascending curve is wholly convex in outline. The culmination of the twitch is characterized by a flat plateau, which terminates with sufficient abruptness to form on the linear record a clearly defined angle. This discontinuity has therefore been referred to as the "angle," and has been observed in the responses of the gastrocnemius and sartorius of the frog and of the tibialis anticus and semitendinosus of cats, and, by F. H. Pratt, in the response of individual sartorius muscle fibres (frog). The significance of the "angle" is discussed in Chapter IX.

The interval between the electrical response and the "angle" has been used to measure the duration of the twitch. The effect of variations in initial fibre length upon the phases of the twitch has been examined, and the results summarized in table 4. The "angle" is a delicate index of the condition of the preparation, especially with reference to fatigue. Modification of the "angle" with fatigue is probably due to asynchronous cessation of activity among the individual fibres of the muscle mass. The curve of relaxation in an intact and unfatigued muscle is concave (upward) in outline, suggesting that a passive process is involved in its production.

At constant initial tension the duration of, and tension developed in a twitch is greatest when no shortening is permitted during activity.

The influence of temperature upon the phases of the twitch is described. The logarithm of the reciprocal of the twitch duration is a linear function of the absolute temperature, the critical thermal increment being about 12,000, and the Q_{10} for 10° to 20°, 2.1. The curve of relaxation, on the other hand has a critical increment of about 6,000, the logarithm of its rate being also a linear function of the absolute temperature. The Q_{10} (10° to 20°) for the rate relaxation is about 1.35. This suggests that the curve of relaxation is a passive process as contrasted with twitch duration, which results from an "active" chemical process.

CHAPTER IV

The Summation of Contractile Responses of Skeletal Muscle

In the intact animal muscular responses may be either prolonged in duration or very brief. The briefest possible response is the single maximal twitch, the characteristics of which we have considered in detail in the previous chapter. Prolonged contractions may be accounted for in at least three ways. (1) It may be assumed that the development of tension in a muscle is brought about by a twitch, and that the tension so developed is maintained by a second mechanism whose function it is to fix a muscle at a given length. This possibility, however, does not concern us in the present chapter and it will be discussed later when considering the problem of muscle tonus. (2) Prolonged contractions may be the result of summation of individual twitches recurring at intervals briefer than the duration of a single twitch (tetani). (3) Prolonged contractions might conceivably result from rotational activity of individual elements; that is, first one fibre or fibre group executes a twitch; later, a second fibre or fibre group responds and so on. In this way a constant small tension might be maintained which is less in magnitude than the tension produced by a maximal motor tetanus. However, the duration of the response represents only one phase of the problem of summation; size of response (*i.e.*, tension developed) is the other important aspect of summation and to this we will first devote our attention. There are two ways in which a muscle may vary its tension development.

1. Multifibre (quantal) summation. Since the all-or-none principle applies to the individual muscle fibre, it follows that the tension developed by a muscle in response to a single stimulus will vary with the number of fibres brought into activity; as Pratt (*784*) has expressed it (p. 27–28), "The discontinuous mode of gradient formation, reflecting as it must the accession or elimination of unit energy values [*i.e.*, fibre responses], has been termed *quantal*. . . . . Compounding of quantals in varied degree is reflected in the graded character of skeleto-muscular reactions in response to varied stimuli." For convenience this variety of summation may be termed "quantal" or "multifibre" summation (*360*); it rests upon the assumption that the individual mechanical tensions of the component fibres of a muscle sum additively (*845*). Multifibre summation has its

parallel in reflex physiology in "spatial summation," which designates the process by which certain reflexes are called forth or augmented by the *addition* of spatially distant units to those already under stimulation.

2. Wave summation. When at constant initial length a muscle "develops a tension superior to that developed in its maximal twitch, there must be at play above and beyond" multifibre summation "that other well-known mode of summation due to fusion of successive contraction-waves within the self-same individual fibres of the muscle" (*845*, p. 111). This for the sake of brevity has been designated "wave summation" (*845*). Since it rests upon the repetition of activity in individual units (being therefore tetanic in nature), it has its parallel reflexly in "temporal summation," by which process certain reflexes, irresponsive to single stimuli, may be evoked if the same stimuli are repeated at certain restricted time intervals through the same afferent channels.

From the standpoint of the delicate gradation and coördination of movement, both types of summation are of equal importance. Since in the past multifibre summation has been the less thoroughly studied of the two, we may consider it first.

MULTIFIBRE (QUANTAL) SUMMATION

The aspects of multifibre summation are twofold. (*a*) When a small group of fibres in a muscle respond simultaneously the familiar *submaximal* response occurs. (*b*) When, however, only a portion of the fibres respond and these fail to respond simultaneously the problem of analysis is more difficult. The simplest case of asynchronous multifibre summation is that occurring when two groups of fibres in a muscle are caused to respond at a brief interval after each other, each group responding synchronously.

Submaximal responses. The facts concerning the mechanical characteristics of submaximal responses are relatively simple. As we have seen, the greater the number of fibres brought into play the greater is the tension developed in the response. It is not known, however, whether the tension developed varies directly with the number of units stimulated, or whether, for example, when one tenth of the number of fibres in a parallel fibred muscle respond the tension developed may be more than one-tenth of that developed in a maximal response. It is likely that the ratio between the tension developed and the number of fibres in activity is not absolutely constant, for when a portion of the fibres in a given muscle is stimulated *it usually develops more tension than it would add to a preexisting response of the remaining fibres in the muscle* (Chapter VI). The reason for this is apparently to be found in the phenomenon described in the last chapter.

that the less a muscle shortens during activity the greater is its tension development. When, therefore, only a portion of the fibres in a given muscle respond they shorten less than when assisted by the remaining

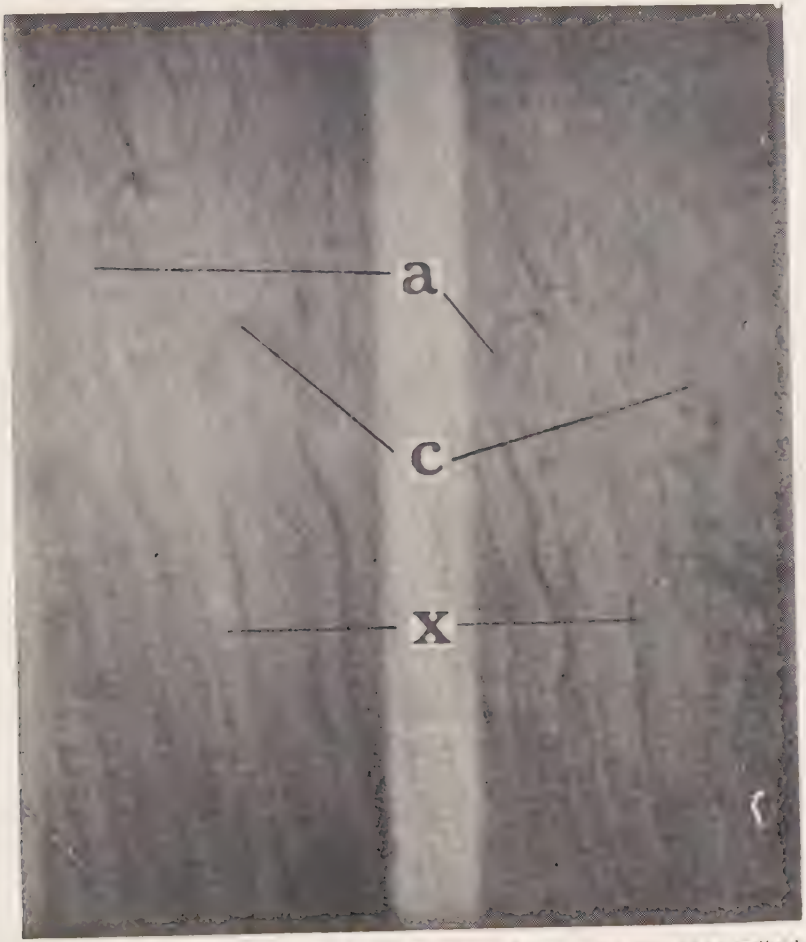


FIG. 42*a*. A photograph obtained by Lisenberger of the contraction of an individual muscle fibre (*x*) in a frog's sartorius, showing shortening of surrounding inactive fibres (right). The left shows *x* resting; *a* and *c* are capillaries (*Inter. Journ. Physiol.*, vol 45, p. 54.)

inactive fibres in the muscle. If the conditions of contraction could be made completely isometric, and the individual fibres could be made to respond simultaneously throughout their entire length, the ratio between the number of fibres stimulated and the tension developed would undoubtedly

be constant for any number of fibres. Owing however to the experimental impossiblity of recording contractions under such conditions, the ratio: $\frac{\text{tension developed}}{\text{number of fibres}}$ tends to become smaller and smaller as multifibre summation approaches its maximal value. It follows from this that submaximal responses are relatively more effective than maximal responses,—a fact which has not yet been duly considered in estimating the efficiency of the contractile powers in experiments upon excised muscle.

Direct demonstration of passive shortening ("crumpling") in fibres adjacent to an active fibre has been given by Eisenberger (*272a*). Figure 42*a* shows one of his photographs of a contracting unit surrounded by undulating inactive fibres. This was obtained from a preparation (intact frog's sartorius) in which the muscle as a whole *did not shorten*. It gives one a clear idea of the large degree of shortening which must occur normally among passive fibre elements in submaximal responses, and emphasises once more that isometric conditions of contraction of the muscle as a whole do not ensure absence of shortening of individual fibres.

Another feature of submaximal responses which strengthens the inferences which we have already made concerning the influence of shortening, is the fact that *a submaximal response is invariably of greater duration than a maximal response*. Thus when only one nerve root of the double (or triple) root supply of gastrocnemius is stimulated the duration of the mechanical response tends to be slightly longer than when the muscle is stimulated maximally (figs. 69 and 70). We have seen that the more a muscle shortens during a single twitch the more brief is its duration measured to the "angle." In a submaximal response the fibres participating shorten less than when assisted by their fellow fibres, as in a maximal response. The summed magnitude of the electrical deflections of the two roots when stimulated singly is, however, approximately equal to the size in mm. of the electrical response evoked by stimulating the two roots simultaneously (*839*, *119*, *358*). This accordingly favours the deduction that the discrepancy in the tension and duration of the mechanical responses results from mechanical conditions encountered *after* the stimulus is over. Similarly it has been found that the duration of the twitches of rectus femoris in response to submaximal shocks were 40.5σ, 40.0σ, 36.5σ, 35.5σ, when the following respective tensions were developed: 800, 800, 1000, 1000 grams.

It may be inferred from these observations that submaximal responses occurring in the body tend to be of somewhat greater duration than maximal responses, their duration increasing, within limits, (*a*) as the muscle length is increased and (*b*) as the number of fibres responding is diminished.

Asynchronous multifibre summation. Only the more elementary cases of asynchronous multifibre summation have thus far been investigated experimentally. The simplest case is that already mentioned in which one group of fibres, A, is excited (synchronously), and the second group of fibres, B, is similarly excited at a brief interval after excitation of group A. This has been accomplished experimentally in two ways. A muscle such as the gastrocnemius having a double root supply may have its roots stimulated one after another and the resulting response analyzed. Since, however, this involves the somewhat remote possibility (Chapter VI) that a portion of the individual muscle fibres may be plurisegmentally innervated by fibres from both roots, an even more simple expedient is to record the

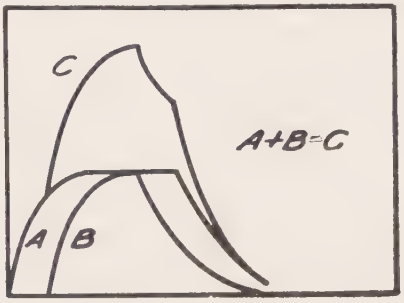


FIG. 43. Asynchronous multifibre summation. Two separate gastrocnemius muscles (same animal) pulling on the same lever, each responding singly at an interval of 12σ, and thus producing a summated response. The curve *calculated* from the single responses taken separately is shown in the figure. Save for the total tension being 5 per cent greater in this predicted curve, the general shape and time relations are in complete accord with the summated curve obtained experimentally. Similar curves have been obtained from a single gastrocnemius preparation responding to successive stimulation of its lumbar roots.

contraction of two separate muscles (*e.g.*, sartorii) attached to the same myograph lever (*841*). The latter procedure of course is open to the objection that the fibres are not in the same muscle mass, and hence have presumably less internal friction to overcome than have a small group of fibres responding within a muscle mass of inert fibres. However, in my experience the results obtained by the two procedures are practically the same which strengthens the inferences made from them.

Let us take as an example a response of fibre group B occurring during the relaxation of a response of fibre group A. If one subtracts from B the remainder of the curve of relaxation of A one finds that the response of B practically coincides with the response which B would produce on an unmodified base-line. In short, algebraical summation results. The declin-

ing tension of response A sums algebraically with the rising tension produced by response B. Such responses are shown in figure 43. Similar algebraical summation occurs when the response of fibre group B falls during the ascent or during the plateau of the response of fibre group A. Very accurate analysis however shows that the statements just made require slight modifications. When the responses are as nearly isometric as they can be made, the algebraical character of the summation is almost absolute. Yet when responses are taken in the ordinary way with levers which permit of several hundredths of an mm. shortening the algebraical character of the summation is not perfect: that is, response B, when occurring during the plateau of A, does not produce quite as large a tension development as when it occurs on an unmodified base-line. In view of the fact that the ratio between the tension developed and the number of fibres responding in submaximal responses tends to decrease with the number of fibres brought into play, it is evident that the lack of perfect algebraical summation is to be attributed to this cause, since muscles shorten more and more as its response approaches the maximal value. An example of the algebraical character of multifibre summation was observed (*48*) in an analysis of the inhibition of spinal and decerebrate knee-jerks. It was often found that the ipsilateral inhibitory break-shock caused a small ipsilateral twitch contraction apparently involving different fibres from those causing the jerk. When such an ipsilateral twitch fell during the relaxation of a knee-jerk a hump was formed which, if carefully subtracted from the curve of an unmodified knee-jerk, closely corresponded in size and in shape to the single ipsilateral twitch occurring on an unmodified base-line (see fig. 104 of Chapter XIII).

Various combinations of fibre groups and intervals of stimulation have been analyzed, always with the same general result of a marked tendency toward perfect algebraical summation. *It is evident from this that under perfect conditions of isometric recording the outstanding characteristics of multifibre (quantal) summation is its algebraical nature.* It is therefore not difficult to understand how a muscle in which a small proportion of fibres respond serially (in such a way that at any given instant over a long period of time the same number of fibres would be in activity) could maintain tension for a long interval without the development of fatigue. We shall see in a later chapter that this type of rotational activity appears to be at the basis of tonic activity, as shown by an analysis of the stretch reflex.

WAVE SUMMATION

Since the outstanding mechanical characteristic of multifibre summation is its algebraical character, analysis is relatively simple, for one need only

subtract (algebraically) from a fused response the curve of an unmodified single response (fig. 43). This is the case at least when the number of muscle groups responding synchronously is limited. Wave summation on the other hand, is not algebraical, as can be shown very simply, and therefore demands a special method of analysis (*360*). Thus when a second maximal response occurs at the "angle" or during the relaxation of a first response, it is completely unmodified by what would have occurred in the first response and starts *de novo* from a new base-line. The general shape, moreover, of such a second response is constant quite irrespective of the point at which it falls during the relaxation of a first response. The declining tension in other words, does not affect it and it certainly does not sum algebraically with it. In the past summated responses of this type had been analyzed on the assumption that the fusion is algebraical in character, and, as we shall see, this has led to unwarranted conclusions regarding the nature of the contractile process (*342*, *440; 301*, p. 183).

It will be convenient in the account which follows to refer to the first stimulus and the first response as "stimulus I" and "response I", similarly "stimuli II, III" and "responses II, III," etc.

When a second maximal stimulus is delivered to a nerve at various intervals following a maximal first stimulus, two contraction waves are set up in each individual fibre of the muscle, and the duration (and size) of the second contractile response varies with the interval between the two stimuli. Moreover it has been found possible to study certain important characteristics of the first response by the modifications which it is capable of producing, as it runs its course, in response II. Thus when response II falls during the plateau of response I the duration of response II is greater than that of I alone and longer than a second response when falling during the relaxation of response I. It has been inferred from this that the durations of response II is under these circumstances augmented by the as yet incompleted processes of response I. A point of considerable interest therefore is to examine the extent of this augmentation in the duration of a second response as it falls at various points in the course of a first response. A few words must first be said however concerning the method of analysis of wave summation.

THE METHOD OF ANALYSIS

Space forbids a detailed consideration of the method of analysis and for this the reader is referred to the original description (*360*). For ordinary purposes it is sufficient merely to determine the duration of the second response, comparing it with the duration of an unmodified first response, or better, with the duration of an unmodified second response

falling after response I has completely subsided. This latter procedure is desirable because, owing to the "staircase effect," a second response tends normally to be briefer than a first. It will be recalled that the duration of a response may be determined with ease and accuracy by measuring the interval between the beginning of the electrical response and the "angle" of the mechanical response, provided of course the mechanical record is scrupulously accurate. *In the present monograph the duration of the response, when spoken of, always refers to this interval.* Now the extent of augmentation of response II produced by an uncompleted response I can be determined very simply by subtracting the duration of an unmodified second response from that of a second response falling at various points in the course of a response I.

It is occasionally important however to determine the *area* of the mechanical response from the linear record. The twitch is of course made up of two variable components, tension and duration, and the product of these has by Hartree and Hill been referred to as the "tension-time." Since the area of an isometric twitch approaches the shape of a rectangle much as does the calibration curve of a galvanometer string in response to a rectangular current (fig. 35), one may take as the area of the twitch the area of the rectangle which it approaches. Careful measurement of such records as those shown in figure 44 (upper figures) have shown that this gives the close approximation to the true tension-time, for area α is approximately equal to area β. The left border of such a rectangle is taken arbitrarily as the normal erected from the commencement of the action current. The right border of the rectangle similarly is taken as the perpendicular dropped from the "angle" of the mechanical response. It is usually found that the tension-time area determined by this rectangular method of analysis varies closely as the duration of the response. Under one important circumstance however they do vary independently, and that is when the "staircase effect" is marked. As shown in figure 97, when the "staircase effect" is pronounced the tension developed is relatively small, and the duration of the response is augmented. The rectangular method of analysis consequently has the advantage of preventing (within limits) errors which arise on account of the "staircase effect." However, it has been found possible by taking certain precautions to avoid the "staircase effect." Thus by placing a muscle initally under a relatively high tension and by causing the muscle to respond several times immediately before recording the summated responses the "staircase effect" can be greatly minimized and sometimes completely avoided. Under such circumstances rectangular analysis is not necessary and safe inferences can be made from determination of the duration alone.

When the method was first described the modifications in response II were divided into four cases according as it occurred. (1) During the ascent, (2) during the plateau, (3) at the angle, or (4) during the period of relaxation of response I. Though of assistance in textual description the division into four cases is somewhat arbitrary and will not be used in the description which follows.

THE INFLUENCE OF A FIRST RESPONSE UPON A SECOND WHEN THE INTERVAL BETWEEN THE TWO IS VARIED

It is scarcely necessary to say that it is essential in making accurate comparisons to use responses from the same preparation, and that the

preparation be kept under as nearly as possible physiological conditions of initial tension, temperature, and circulation, etc. To avoid sources of error arising from submaximal stimulation the stimuli used were always well above the threshold intensity for maximal stimulation.

The general result obtained in an analysis of wave summation is that *the earlier response II falls in the course of response I the more is the duration of response II augmented* (provided of course that response II falls after the refractory phase of I). Thus when falling early in the ascent of response I the augmentation in the duration of II may be 25 to 30 per cent. When falling later in the ascent the augmentation, though considerable, is less marked. When occurring during the plateau the augmentation may be very slight, and toward the end of the plateau it may be impossible to demonstrate augmentation at high temperatures, but it is always demonstrable at low temperatures. When finally response II falls at any point after the "angle" of response I there is no augmentation at any temperature. The "angle," in other words, marks the point at which the first response loses its power of augmenting the duration of the second response. A series of diagrams illustrating these observations is shown in figures 44 and 45. They are plotted directly from records of responses of the intact frog's gastrocnemius at 24°. In these figures both the duration and the tension-time are indicated. As precautions were taken to diminish the "staircase effect" it will be seen that the duration and the tension-time area diminish together.

Usually when II falls, later and later during relaxation of I the tension-time area of response II increases, but in no instance has the *duration* of response II been observed to increase during this period. From this it may be inferred that the increase in tension-time is due to the fact that as the rate of subsidence of the tension of response I becomes less and less rapid, the second response encounters *initially* progressively less of a counter-force. It may, however, be emphasized that this effect is slight and is not to be attributed to an algebraical process for it is far less in amount than would be explicable on the assumption of algebraical summation; moreover, as we have already noted, the general shape of response II is the same wherever it commences along the course of I, which rules out the assumption that the fusion of the two responses is algebraical in character. Further numerical data concerning these observations will be found in the original description (*360*). A numerical analysis of one experiment is given in figures 44 and 45.

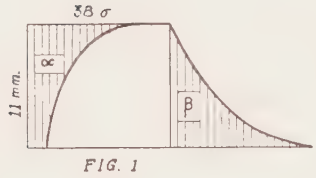


FIG. 1

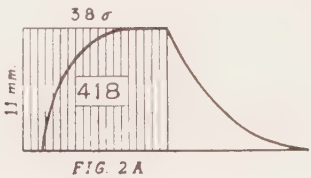


FIG. 2A

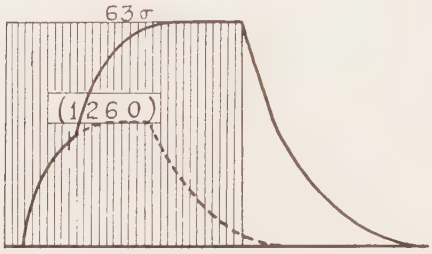


FIG. 2B

CASE I

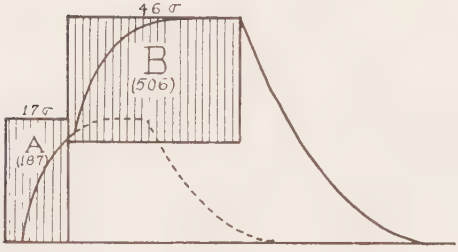


FIG. 2C.

FIG. 44. *Left upper curve.* A twitch of intact gastrocnemius at 24° drawn to scale (enlarged × 1.7) to show that in a maximal twitch area α is nearly equal to area β.

Right upper curve. The same twitch. The shaded area shows the "tension-time," in this case equal to 418. The left boundary of the area is formed by a perpendicular erected from the beginning of the electrical response. The interval between it and shortening (5σ) represents the latent period (Chapter II). The right boundary is a perpendicular dropped to the base-line from the "angle" of the twitch.

Middle curve. A fused response made up of two twitches, the second of which falls during the mechanical ascent of the first. The shaded area represents the tension-time of the total response (1260).

Lower curve (case I). The same, but in this figure the tension-times of the two responses have been analyzed separately as described in the text.

CASE II

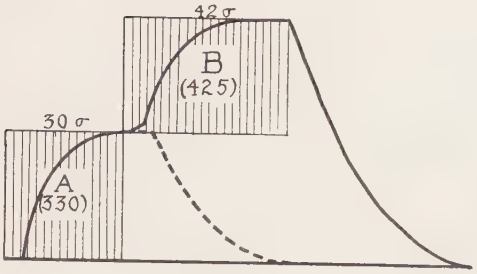


FIG. 3A

CASE III

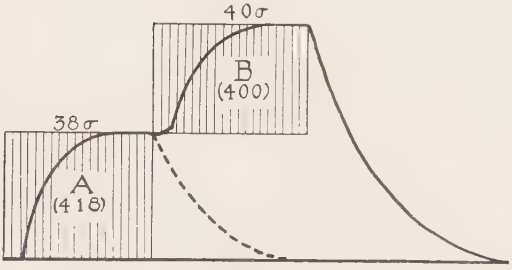


FIG. 3B

CASE IV

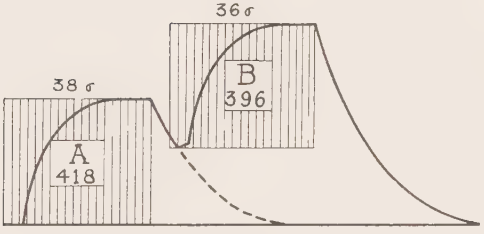


FIG. 3C.

FIG. 45. Case II in which the second response falls during the plateau of response I. The respective tension-times and durations are indicated in the figure. It should be noted that the duration and area of response II is less than in case I.

Case III in which response II fails at the "angle" of response I. Note the period of rigidity.

Case IV in which response II falls during relaxation of response I.

Note the interval of 2σ ("true" latency) during which the relaxation is unchecked; following that is the period of rigidity lasting 3 to 4σ. (All of the responses plotted in figures 44 and 45 were taken from the same preparation, a 30-gram frog at 24°C., the muscle being under 40 grams initial stretch.)

RELATION OF THE "TENSION-TIME" OF RESPONSE I TO THAT OF RESPONSE II

As the interval between responses I and II is increased the relation of the tension-time of the two responses becomes altered. When the interval between the two is of the order of from 3 to 15σ the resulting response is completely fused and has the shape of a large twitch (fig. 44 and 107). One may examine the tension-time of such responses in two ways: either the tension-time of the whole fused response may be measured rectangularly, as shown in figure 44 (middle curve), or one may attempt to separate the two responses in such a way as to estimate the relative area of the part of response I, which occurs before response II, and then to find the area of response II as modified by the remaining portion of I. This latter method of analysis we have already considered, and it is shown diagrammatically in figures 44 and 45. When determined by the first method the tension-time increases rapidly as the interval between the two stimuli is increased. Thus at 14° with intervals between stimuli of 10, 13 and 20σ the total tension-times were respectively 1493 (13.7 grams $\times$ 109σ), 1554 (14.0 $\times$ 111), and 1702 (14.8 $\times$ 115). This indicates that two stimuli become, within limits, increasingly effective as the interval between them is increased. One may now examine the corollaries of this observation. When the interval between the stimuli is 15σ or less, the tension developed is very much less than double that developed by a single stimulus. This is a well-known fact pointed out by many early investigators. When the interval becomes greater, however, *i.e.*, of the order of 20 to 30σ, the tension developed may be double or even more than double that developed by the first stimulus. But if the *duration* of the responses is examined one finds that when a single response has a duration of 40σ, and a second response falls 10σ after the first one has started, the duration of the second response will *not* be 40σ plus the remaining 30σ of response I, *i.e.*, 70σ. On the contrary response II under these circumstances will be only 55 to 60σ in duration. Response I, in other words, is capable of augmenting the duration of response II but the durations do not sum arithmetically. These observations are important since they throw considerable light upon the problem of muscular efficiency.

The tension-time area is, when applied to a muscular response, an indirect measure of the power of doing work (*481*). It is not therefore an artificial conception, for on the basis of a determination of this value one may judge very accurately of the effectiveness of a given contraction (Chapter IX). The power of doing work is of course a function of the duration and the

tension developed by the activating force. In other words, when a muscle pulls upon a heavy body, the *momentum* thereby imparted, will vary with the tension and the time during which the force (muscle) acts. Now from heat determinations, it is known that the energy liberated in the muscle is practically the same for a double response whatever the interval be between the two stimuli, provided of course, that stimulus II falls after the refractory period. But the power of doing work, as indicated by the tension-time, increases very rapidly, and this demonstrates that when two stimuli fall close together, energy is lost. It is for us, therefore, to enquire at what interval a second stimulus may fall and be most effective from the viewpoint of tension-time.

Experiment has shown that a muscle contracts most economically, as judged by the tension-time, when stimulus II falls at the "angle" of response I. This is true whether the tension-time is determined, as shown in figure 44 (middle curve) by taking the rectangular area of the whole summated response, or by determining the tension-time of each individual response separately. Thus in the lower curve of figure 44, in which the tension-time of the responses are analyzed separately, the sum of areas A and B is 693 (187 + 506) when the intervals between stimuli is 17σ. With an interval of 30σ the sum of the two areas is 755 (330 + 425), and finally when response II begins at the "angle" of response I the sum of the two areas is 818 (418 + 400, see fig. 45). When the area of the whole response is determined it is found that after the "angle" the area commences to diminish.

It is evident that these observations are in keeping with Hill's (*476*, *475*) and Lupton's (*669*) demonstration on intact muscle that the efficiency diminishes as the speed of contraction is increased. In other words, when stimuli follow each other with great rapidity in individual nerve fibres, though the energy liberated by each stimulus appears to be the same, the tension developed does not vary directly with the energy liberated within the muscle. Movements, in other words, when performed rapidly, as when responding to rapidly repeated stimuli, require a greater expenditure of energy than the same movement done more slowly.

"THE GENESIS OF TETANUS" (*560*)

It follows from what has just been said that a tetanic response may be generated most economically at a rate of stimulation in which each successive response falls at the "angle" of its predecessor. Thus, we have seen that at a moderate initial tension the duration of the twitch of a frog's gastrocnemius at 24° is about 40σ. It is evident therefore that a rate of

25 per second will give rise to a tetanus in which each successive response should fall approximately at the "angle" of its predecessor. Such a series of responses is shown in figure 46. They have been taken from the same preparation at varying initial tensions. In figure 46 B the duration of the individual responses exactly coincided with the interval between stimuli.

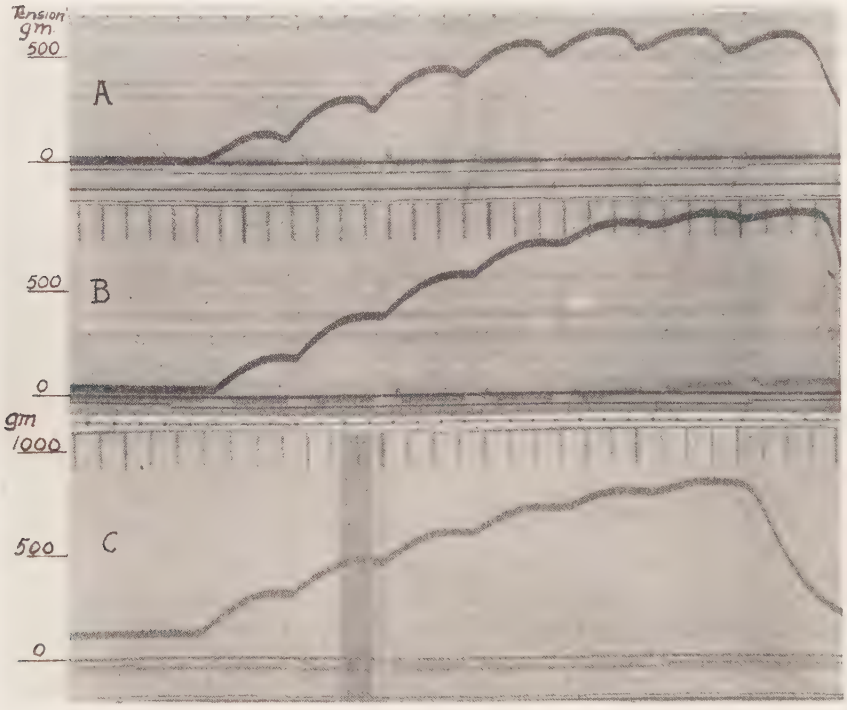


FIG. 46. Responses of the intact gastrocnemius of 35-gram winter frog at 12.5° stimulated at 14 per second. Time above 0.02 second.

A. Muscle slack; initial tension 5 grams.

B. Muscle at 30 grams initial tension.

C. Muscle at 120 grams initial tension.

Note the increasing duration of the individual responses as the initial tension is raised.

This record illustrates an important point which we will have occasion to refer to in a later chapter; namely, that the duration of each successive response tends to become slightly less as the tetanus proceeds. In consequence of this, the duration of the terminal response of a tetanus is less than the duration of the first response or of a single twitch (Chapter V).

We shall see that this is due to the fact of the muscle having shortened slightly during the response.

By increasing the rate of stimulation one may increase the *rate* of the tetanus ascent. But the tension developed is not greatly increased in this way and in a large number of observations it was found that as between

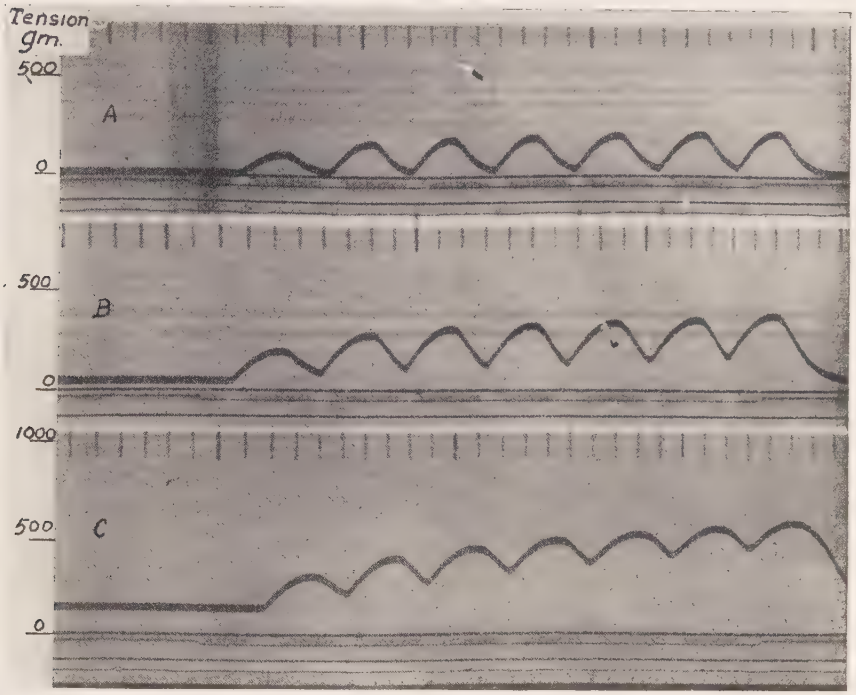


FIG. 47. From the same preparation as the record shown in figure 46 but at 18.0°. Conditions otherwise the same.

A. Muscle initially at low tension.

B. Muscle at 25 grams initial tension. Note increase in duration of the individual responses as compared with those of A.

C. Muscle at 120 grams initial tension. Note the initial convexity of the relaxation n the terminal response.

a rate of 25 per second which would just cause fusion of individual responses and one of 100 per second the increase of total tension developed is usually not more than 5 to 10 per cent (*641*, p. 501; *355*, p. 436). The duration of the ascent, however, might be twice or thrice as rapid at the higher rate of stimulation. Thus in figure 46 B it is 420σ in duration and when

the same preparation was stimulated at double the rate the plateau was reached in 280σ.

In figure 47 responses of the same preparation as that from which figure 46 was taken are shown but at a higher temperature. It may be noted that even though the successive mechanical responses are almost completely separated the electrical responses diminish considerably in size as the stimulation proceeds.

THE PROCESS OF (WAVE) SUMMATION

Time is not yet ripe for an adequate theory of wave summation. Discussion of a summation hypothesis based upon Gasser and Hill's conception of contractile elements responding in a viscous medium has been given elsehwere (*360*), but a judicious reader will find the hypothesis unsatisfactory in many details. It is nevertheless likely that the eventual explanation of wave summation will be based upon the viscous-elastic body conception. One point, however, is clear. The proof that the fusion of individual contraction waves in muscle is a non-algebraical process has made possible a reconsideration of Mines' theory of summation. We have seen that a second response occurring during the plateau of a first commences from a new base line and completes itself quite uninfluenced by what would have happened in the remaining portion of response I. Wave summation therefore cannot be regarded as a simple result of an *accumulation* of H-ions at sensitive interfaces within the individual fibres (Mines). We have found reason for believing that the "angle" of a first response represents the point at which the concentration of ions at these sensitive interfaces becomes abruptly exhausted. Yet if a second stimulus occurs at the "angle" of response I, the second response does not continue at the same level as one would be led to suppose on the H-ion accumulation hypothesis, but a new increment of tension is rapidly developed, as shown in figure 46 B. Ionic accumulation undoubtedly does occur when the muscle is stimulated too rapidly but it is clearly a relatively unimportant factor in the sumation process.

THE PROBLEM OF RED AND WHITE MUSCLE CONSIDERED IN THE LIGHT OF MULTIFIBRE SUMMATION

As the literature on red and white muscle has recently been carefully summarized by Needham (*730*), we need not enter into the historical aspects of the question here. It is sufficient to note that Ranvier (*793*, *794*) and Kroneker and Stirling (*560*) first noted that the duration of contrac-

tion in the red muscle is longer than in the white, and that as a result of this, a higher rate of stimulation is required to produce a fused tetanus in white muscle than in red. The early experiments, however, are to some extent confused by the use of inaccurate recording methods and of excised mammalian muscle. There are vague statements in the literature that red muscle contracts "more" in a tetanus than does a white muscle, by which is presumably meant that red muscle shortens to a greater extent than does white. Recent experiments with intact muscle have not con-

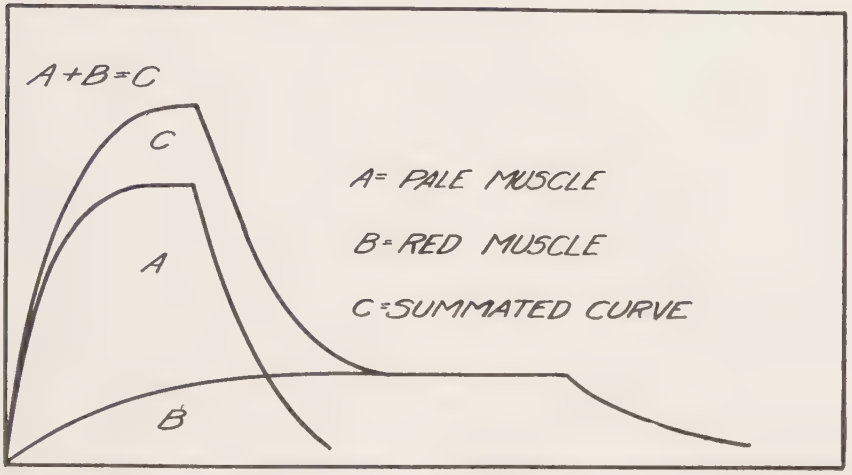


FIG. 48. Multifibre summation in white and red muscle (gastrocnemius and soleus of the cat). The twitches of gastrocnemius alone and of soleus alone are shown in light lines, and the summated curve, when both muscles are stimulated simultaneously and pull together on the same lever, is indicated above (heavy line). Ordinarily the twitch of soleus is about 150σ in duration and that of gastrocnemius 40 to 50σ; gastrocnemius similarly develops 3 to 4 times as much tension as soleus, though in some preparations the ratio was higher than this. In the original records the second "angle" (soleus) was somewhat less precise than that shown in this curve. (Cobb and Fulton, unpublished.)

firmed these early views, and as far as one can determine the ability to shorten is possessed in equal measure by both white and red fibres. It happens that red muscles often have nearly parallel fibres while white muscles are usually pennate, which for purely mechanical reasons results in a greater amplitude of shortening during stimulation of the red muscle. There is no doubt, however, as to the greater duration of contraction (isometric twitch) observed by the early investigators (see especially Hay, *446*), and this is of importance to an understanding of the phenomena of of summation observed in muscles in which there is a generous admixture

of red and white fibres. By glancing at figure 48 one can readily visualize in a twitch the summation effect which results when a white muscle and a red muscle pull simultaneously on the same lever. This helps one to interpret results obtained when a "mixed" muscle (*i.e.*, one with red and white fibres) is stimulated. Grützner (*425*), for example, observed that when a muscle containing both red and white fibres is excited weakly by repetitive shocks of a low rate, an incomplete tetanus was obtained. When, however, the stimuli, though delivered at the same rate, were increased in intensity, the contraction of the muscle increased somewhat and the tetanus became complete. A similar observation has been made with the intact gastrocnemius and soleus of the cat (Cobb and the present writer, unpublished).

We observed, morever, in one or two experiments that the threshold intensity of stimulation of the nerve fibres supplying soleus was apparently higher than that of the fibres supplying gastrocneumius, for as the intensity of the stimulus applied to the mixed popliteal trunk was gradually increased the gastrocnemius muscle was always the first to be affected by the stimulus. In some instances the threshold difference between soleus and gastrocnemius was slight and it could not therefore be regularly utilized experimentally to exclude the soleus during contraction of the gastrocnemius. In one instance, however, a just effective stimulus caused a twitch of gastroncnemius without any apparent contraction of the soleus. When the intensity was increased both muscles contracted and a summated twitch was obtained. The point is now under further observation. The general result of these experiments is illustrated in figure 48. A twitch of soleus is plotted on the same tension-time coördinates as the twitch from gastrocnemius, and the summated tension-time course of the two together is indicated by the heavy curve above the two responses. This has been found to approximate closely the experimental record of summated contraction of these two muscles, demonstrating the algebraical character of the summation effect produced by synchronous activity of red and white fibres in the same muscle group. This observation incidentally gives a rational explanation for the fact not infrequently observed that the twitches of quadriceps femoris of mammals appear to have a gradually ascending plateau, and they are also characterized by a slow terminal portion of the curve of relaxation. It will be seen that both of these effects are explicable in terms of summation of two physiologically characteristic groups of fibres within the muscle. Inasmuch as red fibres are known to occur in quadriceps, it would seem likely that this *is* the explanation.

We shall see in a later chapter (XVI) on tonus that certain authors believe in a special tonic activity of red muscle; they look upon it as possessed of a fixing mechanism quite distinct from the all-or-none lactic-acid contracting mechanism. Our observations on summation show, in the first place, that red muscle contracts and that the curve of its contraction possesses all of the features (*i.e.*, abrupt ascent, flat plateau, and sharp "angle") that white muscle possesses. Moreover, Fletcher (*307*) Embden (see Needham, *730*) and others have shown that red muscle develops lactic acid in response to stimulation exactly as does white muscle, and in addition to that has a higher rate of oxygen consumption than white muscle (*730*). It would seem, therefore, impossible to attribute to red muscle,—save on the grounds of pure speculation,—mechanisms of contraction in any way different fundamentally from the known mechanism of white muscle. When considered in the light of multifibre summation, it is clear that the participation of red fibres in a given contraction adds to the smoothness of the response by virtue of their long duration and the inevitable asynchronism which their participation involves. This was the point of view taken by Ranvier (*793*) who in 1874 first studied the difference between red and white muscle. This is what he says: "L'action des deux espèces du muscles n'etant pas la même, il est possible que leur rôle est different; les pâles, avec leur contraction brusque, seraient des muscles d'action par excellence; les rouges, avec leur contraction plus lente et plus persistent, seraient plutôt équilibrateurs ou régulateurs" (p. 15).

On the basis of multifibre summation it is thus possible to predict with the utmost accuracy, exactly what will be the effect on a given contraction of the participation of red fibres with the white fibres already in activity.

THE RELATION OF THE SO-CALLED "TONUS WAVES" TO THE RHYTHMIC CONTRACTION OF AURICULAR MUSCLE

We cannot in the present monograph enter into the special problems presented by cardiac muscle save in so far as they present features which throw light upon the phenomena exhibited by skeletal muscle. An interesting problem in multifibre summation presents itself, however, in the so-called "tonus waves" observed in the course of rhythmic contraction of tortoise auricle. They were first noted in 1887 by da Fano (*296*, *297*) and since then have been made the subject of investigation by Bottazzi (*131*, *133*), Gruber (*413*), Pereira (*764*), Redfield (*799*) and many others. In the course of a series of spontaneous contractions a slow superimposed contraction is frequently observed. Bottazzi (*131*) suggested that the

phenomenon was explicable in terms of the alleged contractility of muscle sarcoplasm (see below, p. 395). However, with the recognition of special-

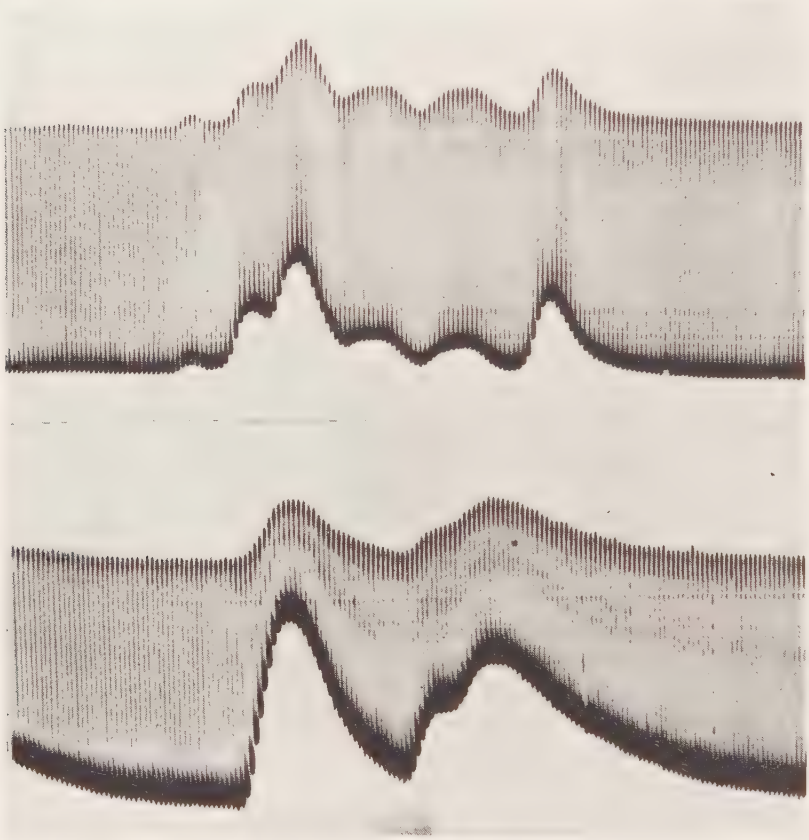


FIG. 49. Rhythmic contractions of auricular muscle of the tortoise exhibiting so-called "tonus" wave, which are probably due to superimposed contraction of the smooth muscle fibres investigated by Shaner (*860*). *Isometric* record. Note that the magnitude of each rhythmic excursion is practically the same during the "wave" as when commencing from the normal base line (Redfield).

FIG. 50. The same as figure 49, but an *isotonic* record. Note that owing to the shortening during the "wave" the amplitude of the rhythmic contractions is greatly diminished (Redfield).

ized regions of smooth muscle around the venous orifices in turtle auricle (Rosenzweig, *821*) extending through the auricle into the ventricle (Shaner, *860*), and with Gruber's observation that the "tonus waves" are

abolished by adrenalin, many investigators are inclined to look upon the superimposed contraction as due to the activity of the smooth muscle strip,—an interpretation early (1903) given by Rosenzweig (*821*). If this be the case it is legitimate to analyze it in terms of multifibre summation, as with red and white muscle.

Redfield (*799*) has recently studied the problem and has obtained the beautiful records shown in figures 49 and 50. He has recorded the rhythmic contraction of the auricle both isometrically and isotonically and observed the alterations in magnitude of the rhythmic responses produced by the "smooth muscle wave" (as we are now justified in calling it). In the isotonic curves the effect of shortening of the auricular fibres is clearly demonstrable in the diminished amplitude of the successive contractions at the height of the smooth muscle wave. In the isometric curves, on the other hand, it will be seen that the magnitude of the successive rhythmic contraction is but slightly altered during the smooth muscle wave, owing to the fact that the auricular fibres remain throughout at practically constant length. It would be difficult to find a clearer demonstration of the effect of fibre length upon the magnitude of contraction. Redfield's observations are as yet unpublished but I am greatly indebted to him for permitting me to reproduce these figures.

SUMMARY

In this chapter various aspects of the problem of summation have been discussed. The designation "multifibre" or "quantal" summation has been used to describe the process by which a muscle alters its tension development through variation in the number of all-or-none contractile units thrown into activity. The outstanding feature of this variety of summation is its algebraical character. Provided the conditions of contraction are completely isometric, the tension development varies directly with the number of units in action. Owing, however, to the experimental difficulty of obtaining completely isometric contractions, when half of the total number of fibres in a given muscle contract they develop more than half the amount of tension which the same muscle develops on maximal stimulation. This is due to the fact that shortening during activity diminishes tension development, and when the whole muscle contracts the individual fibres shorten more than when only half the fibres are active.

The process by which *individual fibers*, through repetition of stimuli at short intervals, develop tension greater than that produced in a twitch (isometric) is referred to as "wave" or "tetanic" summation, owing to the fact that repetitive contraction waves pass along the same fibre. Analysis

of responses involving "wave summation" is rendered difficult because it is not algebraical in character. A special method of analysis involving the determination of the duration of responses is described. A second response occurring in the course of a first is augmented in duration to a greater or less degree according as it occurs early or late in the course of the first response. The degree to which a second response is augmented is believed to be an index of the concentration of activating ions within the individual fibres at the time the second response occurs.

The problem of summation in a muscle which possesses both red and white fibres is considered, and it is shown to be a simple case of multifibre summation in which the duration of activity of the responding constituents varies.

Under the term "asynchronous multifibre summation" is included the most prevalent variety of fusion of contractile tension, namely, that which occurs when fibre responses are spread out in time. This is the condition invariably met in reflex responses. It is pointed out that by rotation of activity of individual constituents prolonged tension may be maintained without the development of fatigue.

Reasons are given for regarding the so-called "tonus wave" occurring during rhythmic contraction of the auricular muscle of the tortoise as due to the contraction of smooth muscle cells known to occur within the auricular muscle. Therefore, this phenomenon too is interpretable on the basis of multifibre summation.

CHAPTER V

Certain Features of the Mechanical Responses of Muscle to Repetitive Stimuli[1]

The mechanical aspects of repetitive responses have been made the subject of innumerable investigations in the past, and the briefest résumé would require an extensive chapter. As von Frey (*343*) and Fenn (*300, 301*) have recently provided us with such an account, it is unnecessary to repeat it here (see p. 107, footnote).

The object in studying the mechanical responses of muscle by an accurate myographic method is to obtain information concerning the nature of the underlying process by which contraction is brought about. In the chapter on the twitch (III) the conditions necessary for obtaining significant mechanical records were enumerated, the fundamental condition being that all the fibre units be made to contract sufficiently in unison to enable one to infer from the recorded response of the whole muscle the course of the response of each individual element. Broadly speaking, however, the twitch is a physiological abstraction, for single responses seldom occur in the intact animal. Movements are the expression of more or less prolonged tetani. In this chapter we will accordingly direct our attention to the nature of tetanic responses.

The general features of tetanic responses are well known. The development of tension is more or less gradual, and the curve representing this process is referred to as the "ascent." The terminal portion of the ascent, *i.e.*, the asymptotic part of the curve which merges into the "plateau," has been referred to as the "ascent-plateau turn" (*637*). The "plateau" itself is flat, and in an unfatigued muscle is parallel to the base line (fig. 51). Since in a short tetanus the "plateau" terminates with the same degree of abruptness as does the "plateau" of the twitch (*355*), we may refer to this discontinuity as the "angle" of the tetanus. Finally, the curve of relaxation of an unfatigued muscle fibre is concave upward throughout its entire extent. We shall see, however, that many curves of relaxation show initially a slight convexity, but this is attributable either to fatigue or to the

[1] The material in this chapter is based largely upon several papers which have appeared recently in the Proceedings of The Royal Society (*351, 353, 355*), but subsequent, previously unpublished observations have been included.

asynchronous cessation of activity of the individual elements. When action currents are recorded simultaneously with the mechanical response, it is possible to investigate another important feature of tetani, namely, the duration of the terminal mechanical response.[2] This is taken arbitrarily as the interval between the beginning of the last action current of the tetanus and the "angle" of the mechanical record. It will be seen that this corresponds exactly to the interval used in the measurement in the duration of the twitch. In simple mechanical records (without electrical responses) the interval between the last stimulus and the tetanus "angle" may be used.

We have seen that the duration of the twitch, measured to the "angle,"

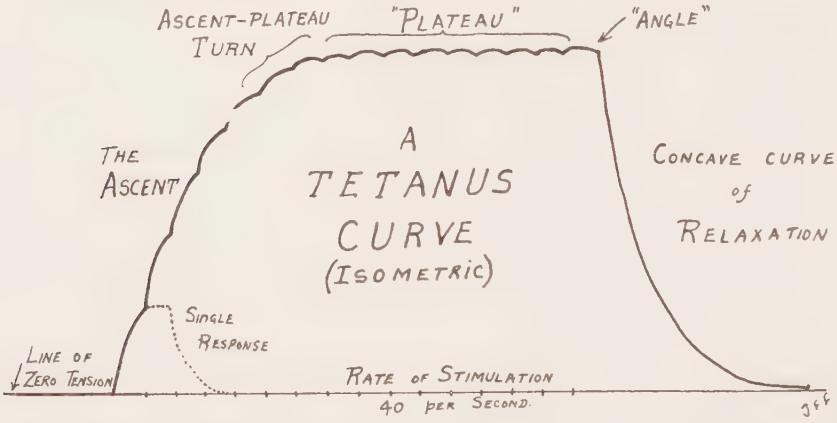


FIG. 51. A diagram showing the features of a tension curve of an isometric tetanus. Plotted from the response of an intact frog's gastrocnemius at 20°, stimulated at 50 per second.

increases as the initial length of the muscle is increased. This, in association with the increased heat production with extension of the muscle, has been taken to indicate that the augmented duration under these circumstances indicates increased energy liberation. In Hill's terminology, more lactic acid is liberated at an initial length of "100" than at an initial length of "70" (*477*), and it appears that a longer interval is required for the dissipation of the acid produced at the greater length. The duration of a given response, therefore, provides, *cacteris paribus*, a rough index of the

[2] In a previous contribution (*351*) the terminal response of a tetanus was designated the "after-action." As this is used as an alternative phrase for "after-discharge" of the central nervous system, confusion is apt to arise from its use. It seems more desirable, therefore, to refer to it as the "terminal mechanical response" (of the tetanus).

concentration of bodies responsible for the development and maintenance of tension. Consequently, it is probably safe to infer from determinations of the duration of the terminal mechanical response of a tetanus the relative amount of lactic acid present within the muscle at the beginning of the response. It will be desirable, however, to consider first the effect of alterations in initial tension upon the general features of short tetani.

THE INFLUENCE OF INITIAL LENGTH

The importance of the initial extension of the muscle in determining the magnitude of the tension developed during contraction was early emphasized in a series of important papers by Blix (*105*). In 1914 Evans and Hill (*291*) observed that the tension developed in contraction rises to a maximum as the initial length of the muscle is increased, and then decreases as the initial tension is raised still further. This was found to hold also for heat production. The result has since been confirmed and extended by Doi (*239*, *240*), who observed that ability of a muscle to do work is similarly dependent upon initial tension, and more recently by Hill (*477*). Patterson, Piper and Starling (*758*) and others (*394*, *1045*) found similar relations for heart muscle, the dependence upon initial extension (venous inflow) having been termed the "law of the heart." Liddell and Sherrington (*637*) noted the same phenomenon in their isometric records of reflex and motor nerve responses of intact mammalian muscle. Often the slightest alterations in initial tension produced two and three-fold augmentation of the tension developed (see Ch. XII, fig. 122). The same observation was also made by the writer on the reflex responses of the semitendinosus muscle of a spinal frog when stimulated by a single break shock applied to one digit on the same side (*351*). Thus at 1 gm. initial stretch the "plateau" of the response was reached at 6 grams, while at 3 grams the plateau height was 12 grams and at 4.5 the "plateau" was approximately 15 grams (fig. 52). Above the reflex curves in this figure are shown the responses to single shocks (maximal) applied directly to the muscle, which incidentally show that the reflex response was repetitive in character. In this experiment it is possible that part of the augmentation of the response with tension is due to proprioceptive influence. For further analysis, one may examine the effect of tension upon the responses of an intact muscle stimulated through its cut motor nerve. For this purpose smoked drum records are sufficiently accurate. The results obtained have, however, been confirmed by the optical method.

If the intact gastrocnemius muscle (active circulation) of a decerebrate frog (*Rana temporaria*) at 20° is stimulated under various degrees of initial

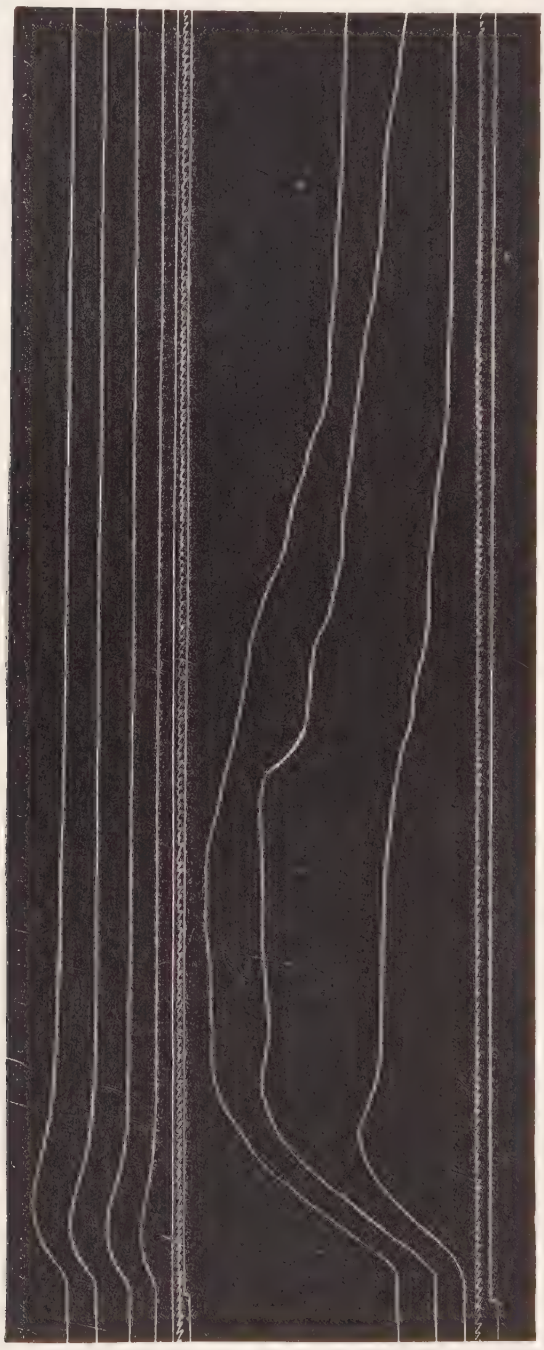


FIG. 52. Showing the effect of increasing the initial stretch upon the reflex (lower curves) and direct responses of the semitendinosus of the frog to single break induction shocks; electrodes for the reflex responses applied to the middle digit of the same side. Preparation spinal and record taken 24 hours after the operation. Temperature 13°. Signal below; time in 0.01 second above (*351*).

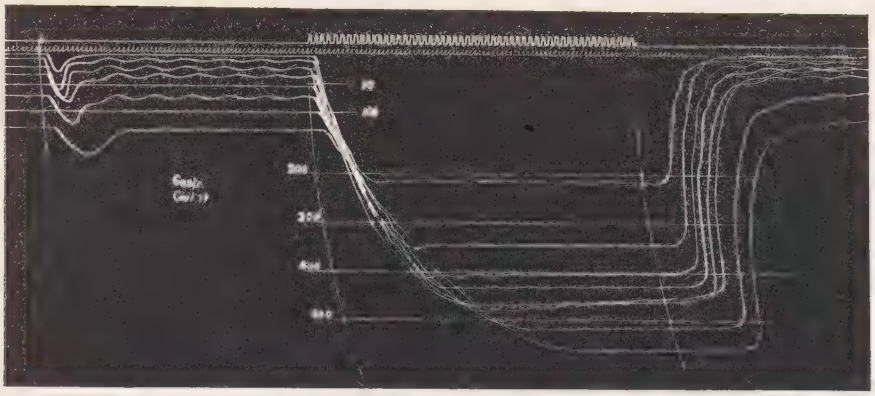


FIG. 53. Intact gastrocnemius of 20-gram frog at 20°C. stimulated at 52 just-maximal break induction shocks delivered through the cut sciatic nerve at 70 per second. A single shock precedes the tetanus (oscillation on the base-line instrumental). Preparation spinal; artificial respiration; circulation vigorous. Stimuli shown by lower signal; time in 0.01 second by the upper. Tendon movement, × 18 (*351*).

TABLE 8

Showing the effect of increasing the initial tension upon the ascent time and upon the duration of the terminal response in two typical experiments

The record of the first experiment is shown in figure 53. The temperature of the second was 11° and the weight of the frog 18 grams, conditions otherwise the same as in figure 53.

INITIAL TENSION	PLATEAU TENSION	TENSION DEVELOPED ABOVE INITIAL	TIME OF ASCENT	AFTER-ACTION (TO HALF-RELAXATION)	RATIO: AFTER-ACTION/ASCENT-TIME
gram	*gram*		*0.001 second*		
5	215	210	140	80	0.57
15	350	235	200	100	0.50
25	410	385	210	110	0.52
40	430	390	240	130	0.54
55	470	415	300	150	0.50
70	480	410	320	160	0.50
100	520	420	400	200	0.50
130	560	430	490	230	0.48
5	255	250	280	160	0.57
10	330	320	330	180	0.54
15	360	345	360	200	0.55
25	380	355	410	220	0.53
35	390	360	450	250	0.55
50	405	355	490	270	0.55
70	425	355	540	280	0.51
85	445	360	620	300	0.49

passive stretch through its cut nerve by a brief tetanic series of just-maximal break induction shocks, the responses exhibit certain important characteristics. The first feature which may be noted in the successive responses (taken at intervals of 5 minutes) with increasing initial length, is the progressive rise in the height of the "plateau." In one experiment (see fig. 53 and table 8) at an initial stretch of 5 grams the "plateau" tension proved 215 grams, while at 40 grams initial stretch the "plateau" tension was 430 grams, or exactly double. From a glance at figure 53, which shows the responses of the gastrocnemius in such an experiment, one will see that the time taken to reach the "plateau" increases markedly with the initial tension; the greater the initial stretch up to about 130 grams the higher the "plateau," and also *the longer the duration of the "plateau" after the cessation of the stimuli.* In other words, the duration of the terminal mechanical response is a function of the initial tension, and by inference of the initial length of the muscle.

These responses were taken with a torsion-wire lever having a frequency of approximately 85 per second, which allowed 2 to 3 mm. shortening of the muscle. Under these circumstances the ratio between the time of ascent and the duration of the terminal response (measured to half-relaxation) gave an approximately constant value (0.50), as indicated in the table. However, with more precise optical methods and employing a myograph which permitted only 0.3 to 0.5 mm. tendon shortening, this ratio was smaller (0.35) and appeared less constant, decreasing as the tension was raised. The importance of the ratio is therefore somewhat problematical.

The degree of tension developed by the intact muscles of a frog is often surprising. The gastrocnemius of an animal weighing to 25 grams, when recording under approximately isometric conditions, will consistently develop 1000 grams tension if stimulated maximally at 30 to 80 grams initial stretch. In view of this relatively enormous tension it is difficult to believe that a maximal response ever occurs when under the control of the central nervous system. A simple calculation makes it evident that such a tension developed simultaneously in both gastrocnemius muscles in 0.1 seconds with 4 to 5 mm. shortening would give a frog weighing 25 grams sufficient velocity to carry it 15 to 20 feet vertically into the air. The gastrocnemius of one 40-gram frog developed 1600 grams, or more than 40 times its own weight. The lamentable frequency with which the tendon breaks during experiments also suggests that such (maximal) contractions do not occur normally in the body. It is interesting that 15 to 20 minutes after excision a muscle which when intact has developed 1000 grams may develop only 500 to 600 grams. Liddell and Sherrington have also directed attention to the large tensions developed in motor tetani of the quadriceps

of the cat (*637*), and it has since been observed (*365*, p. 585) that this muscle may develop as much as 40 to 50 kilos, *i.e.*, 25 times the weight of the cat. Gasser and Dale (*218*, *388*), moreover, observed tensions as great as 25 kilos in the cat's gastrocnemius even when the conditions of contraction were not completely isometric.

FACTORS INFLUENCING THE DURATION OF THE TERMINAL MECHANICAL RESPONSE OF A TETANUS

The duration of the terminal mechanical response of a tetanus is influenced by five important conditions: (1) the initial length of the fibre; (2) the extent of shortening permitted during contraction; (3) the duration of the tetanus (*i.e.*, the number of stimuli delivered at a constant rate); (4) the rate of stimulation; and finally (5) the temperature. It will be necessary to consider each factor separately, and it may be assumed in the description of any one factor that the other four remain constant. After considering these five conditions, the relation between the duration of the twitch and the terminal mechanical response will be discussed.

1. The initial length of the fibre. Other things remaining the same, the greater the initial length of the muscle fibre (within physiological limits) the greater is the duration of the terminal mechanical response. This, as we have already noted, is illustrated in figure 53. The responses in this record were obtained with a lever which permitted 2 to 3 mm. shortening of the muscle in each response. In view of the fact that gastrocnemius is not parallel-fibred, it is evident—for purely mechanical reasons—that at the shorter initial length the extent of shortening of individual elements during the contraction will be somewhat greater than at greater initial lengths where the tensile forces are developed more nearly along the longitudinal axis of the muscle. However this may be, at the greater initial lengths the actual extent of the shortening of the muscle as a whole, as distinguished from the individual muscle fibres, is greater because the tension developed is greater. From the viewpoint of the individual muscle fibre, therefore, these two effects being in the opposite direction tend to neutralize each other. It is, therefore, a just inference that the actual amount of shortening occurring is of the same order of magnitude at all initial lengths.

It will be seen in figure 53 and in table 8 that the duration of the terminal mechanical response varies from 80 to 230σ *i.e.*, nearly 200 per cent.

An interesting application of the enhanced duration of the terminal response of a tetanus at high initial tensions is shown in figure 54 in which 14 stimuli were allowed to lapse during the tetanus "plateau" at various

initial stretches. As will be seen in the figure, the depth of the notch caused by the excision of stimuli at 30 grams initial stretch was 80 per cent of the "plateau" height; at 75 grams it was only 60 per cent of the "plateau"

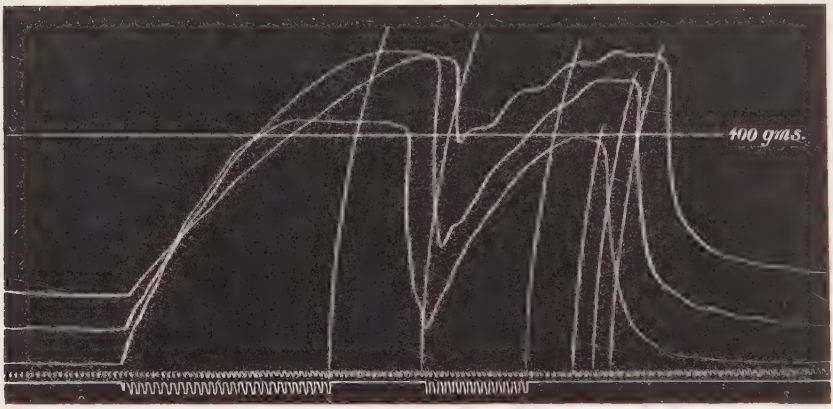


FIG. 54. Unexcised gastrocnemius; circulation vigorous; temperature 14°. Stimulated indirectly by 29 just-maximal stimuli, as in figure 53, at 70 per second, but followed by a pause and then 14 stimuli. Initial tension varied (30, 75, and 130 grams). Lower signal shows the stimuli; the upper time in 0.01 seconds (*351*).

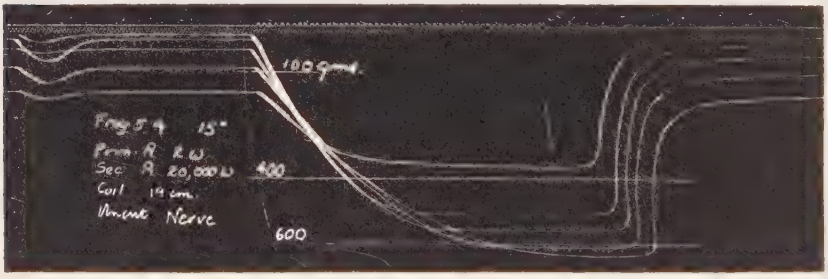


FIG. 55. Successive tetani with increasing initial stretch taken under exactly the same conditions as the responses shown in figure 53 save that the nerve was *uncut*. A strength of stimulus was used which was just maximal for the efferent fibres without being adequate for the afferent fibres in the mixed trunk.

height, and at 120 grams only 26 per cent. In view of the greater mechanical tension at the second and third "plateau" levels, this result would be difficult to understand were it not for increased energy liberation at these levels. It is noteworthy in these curves that when the stimulus ceases

before the "plateau" is reached, the curve continues for a time to ascend *and then becomes level for a short period before relaxation commences.*

Since it is possible in a frog to employ a strength of stimulus which is adequate for motor fibres in the uncut sciatic trunk without affecting the sensory fibres (Lutz, *670;* see also, *349*), it became a problem of interest to determine whether or not the cutting of the nerve altered the duration of the terminal response.[3] In view of Madame Lapicque's (1923) demonstration that the chronaxie of the sciatic nerve increases immediately it is severed from the higher centres of the brain (*615*), it seemed possible that the response with the nerve intact might differ from that with it cut. In figure 55 responses are shown taken under exactly the same experimental conditions as indicated in figures 53 and 54, save that the nerve was intact. The reflex condition of the preparation was such that the slightest tap on any one of the digits on the side used for experiment caused a vigorous flexion reflex. During the response to stimulation of the uncut nerve there was no visible evidence of reflex activity, which is adequate ground for believing that only motor nerves were being stimulated. Responses were taken in this way immediately before and immediately after section of the nerve, and in none of the six experiments performed (smoked-drum) was there any apparent difference in duration in the terminal responses. This has since been confirmed by the optical method in which the electrical responses served as a control for the absence of reflex activity. It may be concluded from this that the cutting of the nerve, *i.e.*, severing the axon from its cell body, does not modify the characteristics of tetanic responses.

2. Shortening during contraction. If increasing the *initial* length enhances the duration of the terminal response, it should be possible similarly to vary the duration of the last response by permitting varying amounts of shortening *during* the tetanus, the *initial* length remaining constant. This was tested in a series of 15 experiments. It was found, as anticipated, that the more nearly isometric the conditions of contraction were made, the greater was the duration of the last response. Thus, in the experiment shown in figure 80 (Chapter VII), when the shortening during the response was 0.05 mm. the terminal response lasted 155σ, while with 1.03 mm. shortening the terminal response was only 95σ in duration. Similarly in figure 81 with a tetanus of two responses, the last response was 82σ when the shortening was 0.02 mm. and 63σ with ± 0.50 mm. shortening. The interpretation of these observations, however, is not obvious as at first sight it might seem, for the same phenomenon occurs in a single twitch; that is to say, at constant initial length, the greater the shortening during the contraction, the more brief is the response (Chapter III). In the twitch the effect is apparently one solely upon the *rate* of dissipation of the lactic acid, rather than on the magnitude of its production, for, according to our present conceptions, the amount of lactic acid liberated by a stimulus is determined by the

[3] These observations have not previously been published.

length of the fibre at the moment at which the stimulus is delivered (*361*). It would appear likely, therefore, that the altered duration of terminal tetanic responses with varying degrees of shortening is a combination of two effects, namely, an effect of length of fibre *per se*, *i.e.*, upon the magni-

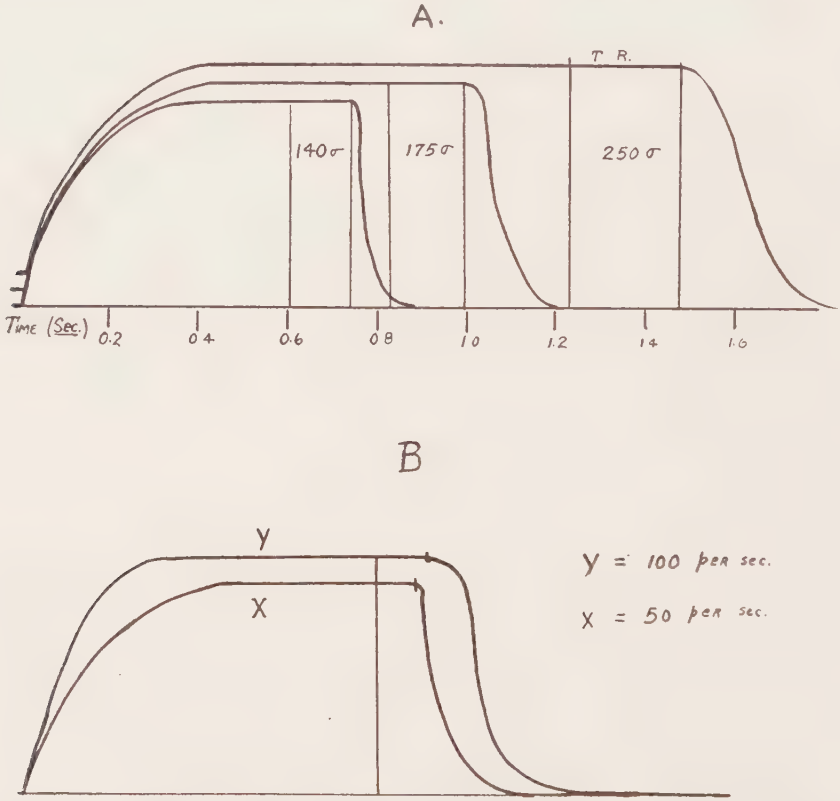


FIG. 56. A. Diagram showing the effect on the terminal mechanical response of a variation in the duration of a tetanus, the rate of stimulation being constant. Curves drawn from response of intact frog's gastrocnemius at 20°.

B. The same showing the effect of variation in the rate of stimulation, the duration being constant.

tude of the lactic acid production by each stimulus, and (2) a second effect upon the rate of dissipation of the acid. As both work in the same direction, it is impossible to separate them. In fact if it were not for the known increased initial heat production with increased extension, there would be no reason for not attributing the increased duration entirely to the second cause.

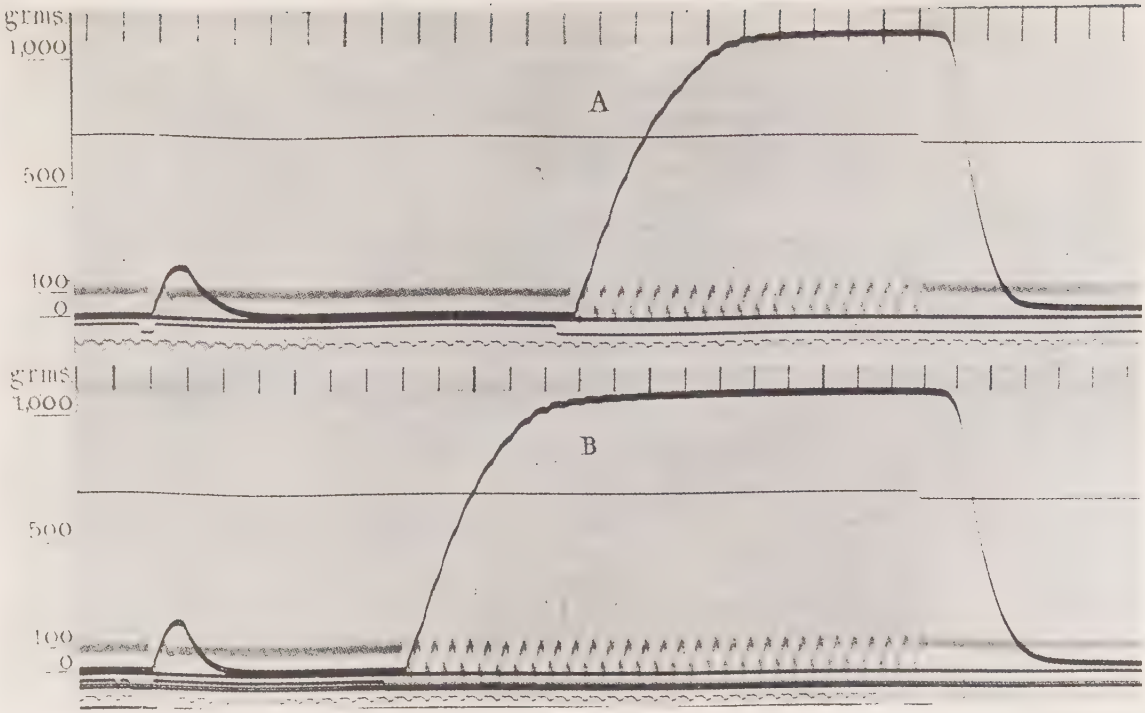


FIG. 57. Responses of intact gastrocnemius of frog at 23.5° showing the effect on the terminal "angle" of the tetanus of increased duration of stimulation (constant initial tension; 25 grams). String tension 55 mm. per ampere. Time above = 0.04 second.

A. Duration of plateau, 0.38 second. The twitch in this record being the first response of the muscle after a rest is "abnormal," as described above, figure 36 D.

B. Duration of plateau, 0.58 second. Note slight rounding of the terminal angle. Here the twitch is normal (*355*).

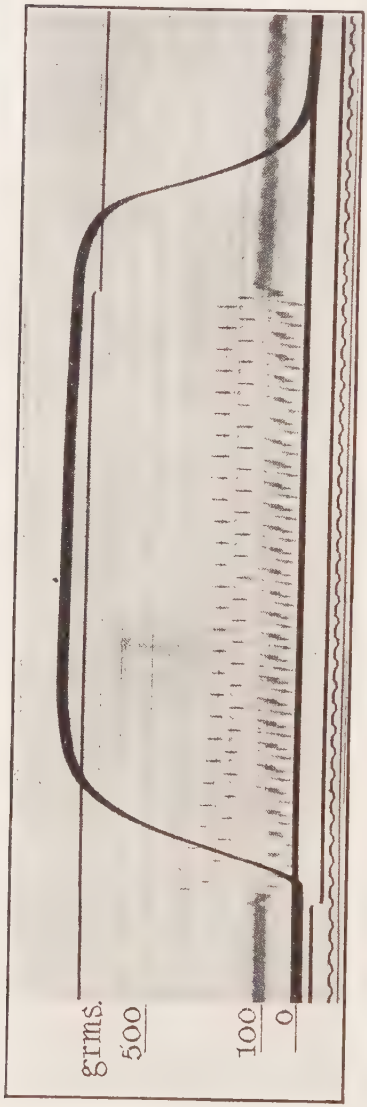


FIG. 58. Gastrocnemius at 20° stimulated at 100 per second. Though 2.0 mm. shortening occurred, which in itself would tend to cut down the energy liberated, the relaxation, nevertheless, shows the signs characteristic of severe fatigue. The previous response of this preparation was at 50 per second and exhibited a sharp angle (355).

3. Duration of the tetanus. Other conditions being constant, the greater the duration of the tetanic response the longer the terminal mechanical response. The augmentation in the duration of the terminal response with prolongation of the tetanus is most marked between durations of 0.10 seconds and 2 seconds. Thus, in a tetanus of 0.10 seconds at 20° the duration of the terminal response may be only 35σ. In a tetanus of 1.0 seconds the duration would be 100σ, and in one of 2 seconds 160 to 170σ. At 5 seconds the duration would be of the order of 300 to 350σ. A diagram illustrating the influence of stimulus duration is shown in figure 56 A. An actual record obtained in such an experiment is given in figure 57. In A the tetanus duration was 0.38 second and in B 0.58 second, while the respective durations of terminal response were 38 and 42σ. This again is taken to indicate that the rate of production of lactic acid in a tetanus, *e.g.*, at 50 per second, is more rapid than the rate of its dissipation. The result of this is inevitably an accumulation of acid within the fibre.

4. Rate of stimulation. By increasing the rate of stimulation—the duration of the tetanus remaining constant—it is possible to prolong the terminal response. Thus, when stimulated at 40 per second for 0.38 second the terminal response lasts 46σ. In a response of the same preparation taken immediately before (or immediately afterwards), but stimulated at 80 per second for the same interval (0.38 second), the duration of the terminal response was 65σ. If our working hypothesis is correct, this provides direct evidence that more lactic acid is produced by a tetanus of 80 per second than is produced by one of 40. A diagram of this effect is shown in fig. 56 B. But if the rate of stimulation is enhanced to above 100 per second, the duration of the last response again falls (in tetani of 0.5 second duration or longer), and the "angle" becomes markedly rounded (fig. 58). The smothering of the "angle" under these circumstances, together with the shortening of the terminal response, raises an important question. Shortening of the terminal response cannot be attributed to an accumulation of acid ions within the fibre, for when this occurs, as in prolonged tetani (at a lower rate), the terminal response is lengthened. Some other factor, possibly indirectly dependent upon the exixtence of fatigue, must be sought for. As we shall see below, this new factor is probably the lapsing effect, which Pratt (*781*, *784*) observed in individual fibres stimulated repetitively with the pore electrode.

The inferences drawn from the augmented duration of the terminal response may appear somewhat out of harmony with those drawn by Hill (*472*) from his experiments on varying rates of stimulation. He observed in isolated sartorius preparations stimulated directly, that the magnitude of the heat liberation per unit tension is constant be-

tween rates of stimulation varying from 17 to 100, and from this he concluded that the amount of lactic acid liberated per unit tension was constant. In his words, "the rise of tension is due to the presence of chemical substances, liberated in conjunction with heat by the processes called forth by excitation. The presence of a definite amount of these substances in the neighbourhood of certain surfaces or interfaces in the muscle, calls forth the same amount of tension independent of the exact rate at which the stimuli occur. These chemical substances are removed or destroyed at a rate proportional to their concentration at any moment; and, therefore, if they are produced (and removed) at a greater rate by an increased frequency of excitation, their concentration in the muscle must be increased proportionally. This increased concentration, however, is accompanied by an increased tension, and, therefore, the tension developed remains proportional to the rate of heat-production."

This apparent discrepancy can be accounted for in either of two ways. In the first place, it is evident that the conditions of two experiments were widely divergent, and furthermore there is no proof, when one stimulates an isolated muscle in Ringer solution at 100 per second, that all of the individual fibres respond at that rate. Pratt's results, in fact, lead one to suspect that fibres would not respond at such a rate for a long period. I have occasionally observed that when an excised muscle is stimulated at 100 per second it responds at half the rate, *i.e.*, at 50 per second.

There is another possible explanation, however, and one which on many grounds appears the more important. Inasmuch as the glycogen lactic-acid reaction is reversible and therefore subject to mass effects it is necessarily self-limiting, *i.e.*, when acid has accumulated within the fibre during rapid stimulation the amount liberated by each successive stimulus becomes less and the tendency for the acid, already free within the muscle, to become reformed into glycogen becomes increasingly great as the acid concentration rises. This being the case, it is conceivable that the heat production would remain more or less constant at progressively increasing rates of stimulation. This is substantially the explanation which Hill urges.

5. Temperature. The influence of temperature on the duration of the terminal response might be anticipated from our observations on the twitch, *i.e.*, the lower the temperature the greater the duration of the terminal response. The Q_{10} for 10 to 20° is of the same order of magnitude as that of the twitch. We will refer to this again at the end of the chapter.

A COMPARISON BETWEEN THE DURATION OF THE TWITCH AND THE DURATION OF THE TERMINAL RESPONSE OF A TETANUS

Gad and Heymans (1890) noted that the after continuance of the tension, following cessation of stimuli in a tetanus, is of about the same duration as the twitch (*372*). Since the duration of the terminal response is increased by raising the initial length of the muscle, and since the duration of the twitch is also increased with initial length, the relation between these two phases of muscular activity at once presents itself.

To make the records of twitch and tetanus strictly comparable, the twitch was recorded on the same photographic plate as the tetanus, preceding the latter by a brief interval

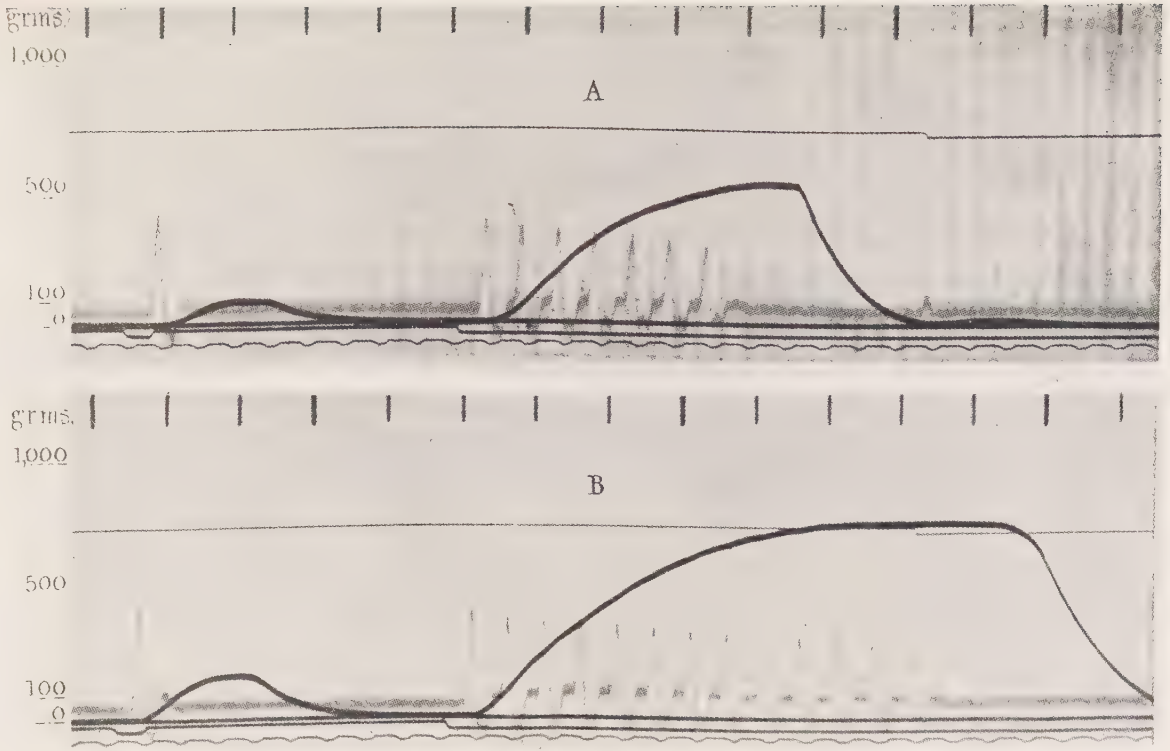


FIG. 59. Responses of intact gastrocnemius of 30 gram frog at 15° to short tetani preceded by twitch. String tension 40 mm. per ampere. Time above = 0.04 second. Plate falling at 30 cm. per second (*355*).

A. Initial tension 5 to 7 grams. Tetanus composed of 7 stimuli. Cessation of stimuli not signalled (done by hand by breaking primary circuit). Note sharp terminal "angle" of tetanus.

B. Initial tension 8 to 10 grams. Tetanus composed of 13 stimuli. Note modification of the "angle."

varying with the speed of the plate. To examine the effect of initial tension upon the twitch and after-action, successive records were taken from a freshly made preparation at intervals of from four to five minutes. The tension was increased in small increments for each successive response, but to ensure complete recovery between them (as passive tension interferes with the circulation) the tension was relaxed immediately the response

TABLE 9

Showing the relation of the twitch to the tetanus (intact gastrocnemius of 30-gram decerebrate frog); duration of tetanus, 0.38 second in first preparation, and 0.54 second in the last

INITIAL TENSION	TWITCH			TETANUS			RATIO OF TWITCH/ TETANUS TENSIONS
	Tension developed above initial	Duration to "angle"	Rate of proportional fall (to half-relaxation)	Tension developed above initial	Duration of terminal response	Rate of proportional fall (to half-relaxation)	
			Preparation at 23.5°				
grams		*0.001 second*			*0.001 second*		
5?	113?*	39	11.3 (10)	680	37	34.0 (20)	0.166?
34	150	40	11.5 (13)	1023	40	33.0 (31)	0.147
57	187	42	11.7 (16)	1084	43	32.9 (33)	0.173
110	198	44	11.6 (17)	1094	45	32.0 (33)	0.181
172	186	46	11.7 (16)	983	47	31.0 (32)	0.190
218	178	48	11.1 (16)	872	48	29.1 (30)	0.204
25	165	40	11.7 (14)	1025	41	33.0 (31)	0.161
			Same preparation at 19°				
5–10	113	49	9.4 (12)	972	50	27.7 (35)	0.116
45	173	57	9.1 (19)	1125	58	27.3 (41)	0.154
110	181	63	8.6 (21)	1067	74	26.6 (40)	0.166
175	170	63	8.5 (20)	953	79	21.2 (45)	0.176
			Another preparation at 25° (Frog same weight)†				
38	162	36	13.4 (12)	1069	38	31.4 (34)	0.151
73	191	40	12.8 (15)	1132	42	31.4 (36)	0.169

* Twitch "abnormal," as described in Chapter III, figure 36D.

† These two responses are shown in figure 60.

had ceased. At the end of the experiment, as a control, a record was taken of a response at a small initial tension corresponding with the first one of the experiment. The isometric lever permitted on an average 0.4 mm. shortening.

Experiments (of which 20 have been performed successfully) reveal that the duration of the twitch measured by its "angle" is (at all initial tensions)

invariably somewhat greater than the duration of the corresponding terminal response of a tetanus, provided the tetanus be less than 0.2 to 0.3 seconds (*i.e.*, 10 to 15 stimuli at 25 to 30 per second) in duration. Thus, in figure 59 A, showing a record taken on a relatively "fast" plate (30 cm. per second), the duration of the twitch is 65σ, while the duration of the corresponding terminal response of the tetanus—in this case composed of seven responses at 30 per second—is only 50σ. It is noteworthy that this tetanus ends with a particularly sharp terminal "angle." Figure 59 B shows the following response of the same preparation at slightly higher initial tension, in which the tetanus was composed of 13 responses. The duration of the twitch is 66σ, and the terminal response 60σ. In this record, though the mechanical tension is greater, the subsidence angle is less sharp. On increasing the duration of the tetanus slightly more (0.4 seconds) the duration of the terminal response becomes equal, or very nearly so, to the duration of the twitch (see table 9).

A duration of tetanus was chosen which at relatively small initial tensions was characterized by a terminal response of the same duration as that of the twitch. Successive records were then taken at increasing initial tensions. These experiments have demonstrated that so long as the muscle remains fresh and relatively unfatigued, the duration of the twitch remains equal to that of the terminal response of the tetanus at all initial tensions. Thus, in the experiment summarized in table 8,[4] at 34 grams initial stretch (23.5°), the duration of twitch and after-action were each 40σ, while at 218 grams stretch their durations were 48σ. A feature of the experiment is the control observation in which, on returning to 25 grams stretch, after subjecting the muscle to relatively severe tensions, the duration of the twitch is again 40σ and of the corresponding terminal response, 41 to 42σ. With a somewhat more prolonged tetanus (0.5 to 0.6 second), even in a fresh preparation, the terminal response always becomes longer than the twitch. Two records in which this is illustrated are analyzed at the bottom of table 9, and the responses themselves are reproduced in figure 60.

FACTORS INFLUENCING THE CONFIGURATION OF THE TETANUS "ANGLE"

We have just noted that when a muscle is stimulated at a high rate for a short period, the commencement of relaxation is frequently characterized

[4] To make the analysis of the electrical responses given in tables 4 and 11 strictly comparable with the results in table 9, the measurements have all been taken from the same experiment. The twitches reproduced in figure 38, Chapter III, are also from this experiment.

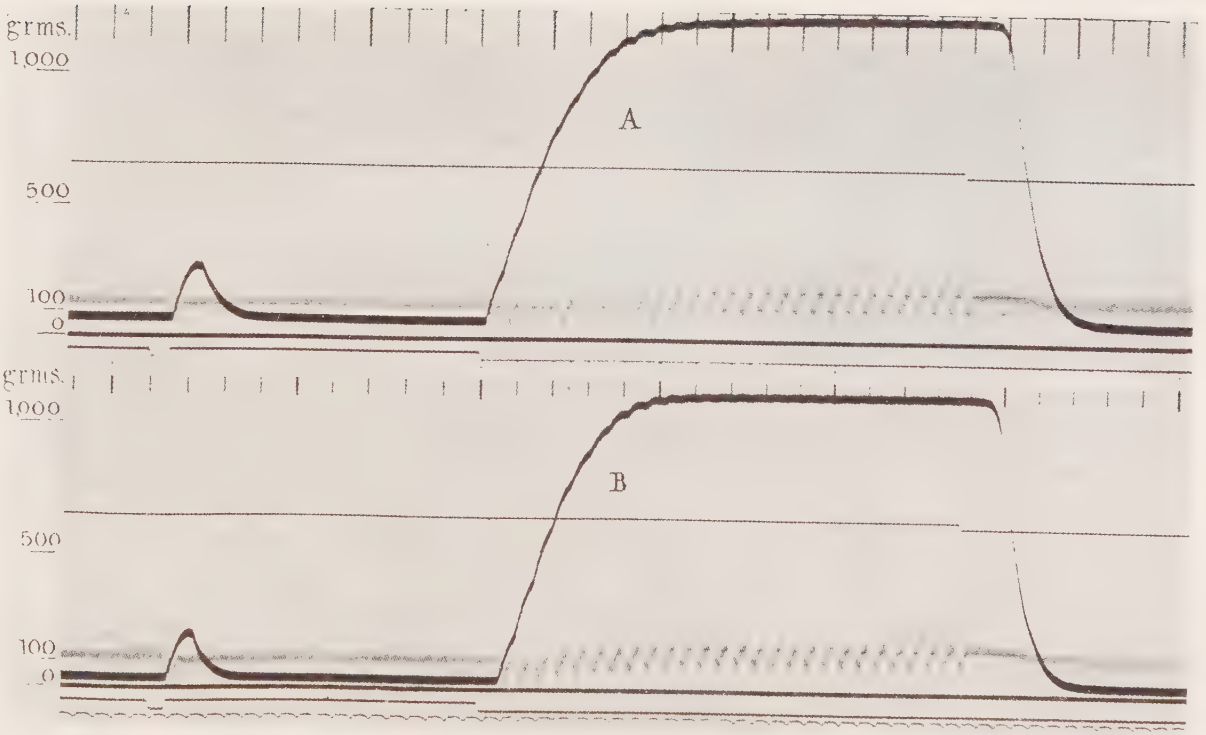


FIG. 60. Responses of intact gastrocnemius of 30-gram frog at 25° to a short tetanus (0.54 second) preceded by twitch. String tension 42 mm. per ampere at magnification of 285. Time above = 0.04 second. Plate falling at 15 cm. per second (*355*).

A. Initial tension 73 grams. Scale of tension on left.

B. Initial tension 38 grams. For further analysis of curves see the bottom of table 9.

by a rounded "nose"[5] in place of the normally precise "angle." This leads us to consider the factors which influence the sharpness of the "angle." It will be seen in figure 59 A that a brief tetanus of a low rate is associated with a sharp "angle" and a completely concave curve of relaxation. Pratt (unpublished), moreover, has recently found evidence, in a series of beautiful experiments, that the curve of relaxation of a tetanus of a single muscle fibre is characterized by a similar abrupt commencement and ensuing concave course. We may reasonably infer, therefore, that tetanic responses of the whole muscles are made up of individual fibre tetani with sharp "angles" (cf. Chapter III, p. 115). This being the case, how are we to account for the initial "nose" found so commonly in tetanic responses of the whole muscle? It will be convenient to discuss the experimental evidence under

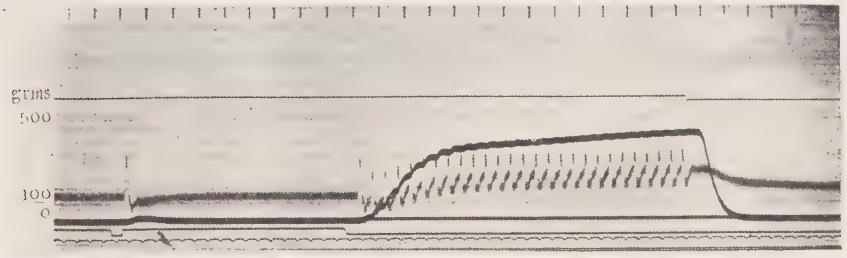


FIG. 61. Response of gastrocnemius of 30-gram frog at 24°, in which 3 mm. shortening was permitted before developing appreciable tension. Note the precise nature of the terminal "angle" (*355*).

the five headings used in elucidating the factors which influence the duration of the terminal response. The observations have been made upon intact muscles with normal blood supply.

1. Other things remaining constant, alterations in initial length have but a slight effect upon the "angle." In many responses those at the greater length appear to have a slightly less abrupt "angle" than at a shorter length (fig. 60).

[5] Attention was first directed (1874) to this feature of the curve of relaxation by Funke (*366*), and later writers have accordingly referred to it as "Funke's Nose." Working with excised muscle, he observed that the nose became increased in prominence as the muscle became fatigued. Many investigators have speculated concerning the causation and significance of the nose, some having attributed it to activity of the sympathetic nervous system (*113*). However, there is little ground for this belief (Chapter XVI); and as we shall see temporal dispersion of fibre activity is almost certainly its cause. When a temperature gradient exists along a muscle Funke's nose is particularly prominent. (Unpublished observations.)

2. The influence of shortening during contraction has a very marked effect on the configuration of the "angle." Under complete or nearly complete isometric conditions, the "angle," in my experience, is invariably sharp, and in short tetani at 20 to 60 per second there is practically no initial "nose" at the commencement of relaxation (figs. 59 A and 61). The more the shortening permitted during the contraction, the greater is the modification of the initial portion of the relaxation curve (figure 80, Chapter VII). This has been attributed to the unequal extent of shortening among the individual constituents of the diagonal-fibred muscle (*361*),

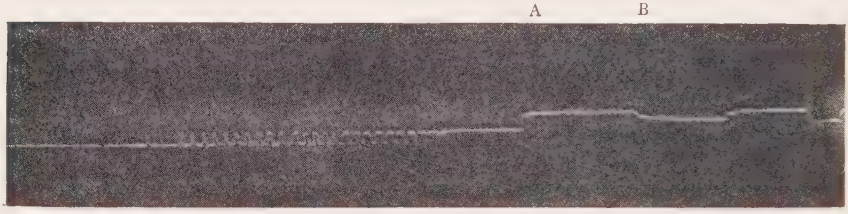


FIG. 62. An unpublished record obtained by Dr. F. H. Pratt of tetanic respones of a single muscle fibre. The early responses are twitches which are followed by increasingly prolonged tetani until complete fusion occurs. A new fibre or fibre group comes into activity at A and ceases at B. Note the precise character of the termination of the response.

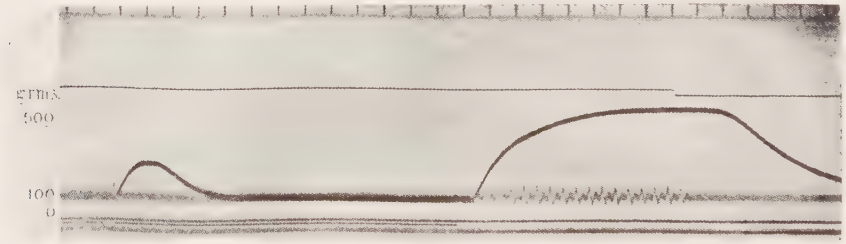


FIG. 62*a*. Showing the responses of gastrocnemius 15 minutes after the circulation to the muscle had been cut off; note the delayed relaxation. Temperature, 17° (*355*).

which necessarily occurs when the muscle as a whole shortens. The result of this inequality is that some fibre elements will cease to contract before others and asynchronous cessation of activity ensues (Chapter III).

3. The duration of the tetanus has likewise a marked influence. The briefer the tetanus, the sharper the "angle" and the less the initial "nose." Responses illustrating this are shown in figures 59 A and B and 58. In very long tetani, even when at a low rate, the terminal "angle" may be completely smothered. The explanation of this effect is more difficult. Clearly, it is a process associated with mild degrees of fatigue, for—*caeteris*

paribus—the longer the muscle is stimulated, the greater the opportunity for the development of fatigue, and hence the more extensive is the modification in the tetanus "angle." But it is important to decide whether this effect is an expression of a corresponding condition in each individual fibre, or whether it is in some way associated with asynchronous cessation of activity of the fibre units. In the complex assemblage of the average muscle it is extremely difficult to believe that in a prolonged stimulation each individual unit would have liberated within it exactly the same amount of acid. In other words, on purely statistical grounds it is inherently unlikely (and it becomes increasingly so as the duration of stimulus proceeds) that each fibre unit would cease contracting at the same instant. Consequently, though we have as yet no direct proof, it is likely that asynchronous cessation of activity is the more important factor of the two. In this connection Dr. Pratt has very kindly informed me that the cessation of contraction of individual fibre tetani, even when prolonged, is invariably sudden. This is illustrated in figure 62, which Dr. Pratt has kindly permitted me to reproduce. This also is in keeping with the previous conclusion.

4. The rate of stimulation also modifies the "angle." Other things being equal, the greater the rate the more rounded the "angle." Here again, the statistical influence is to be reckoned with and one would anticipate that the greater the number of stimulations in a given interval the greater would be the tendency for inequality of effect among the individual constituents.

We have already alluded to an important secondary effect observed at high rates of stimulation, namely, a *shortening* of the terminal response. This cannot be explained on the grounds of fatigue alone. Some other factor possibly associated with fatigue must be invoked to explain it. A possible explanation suggests itself from Pratt's observation, that when a muscle fibre is stimulated continuously for a given time the excitability soon rises above the threshold stimulus, and activity then ceases abruptly. In his words, "If fatigue imply lowering irritability it may be assumed that the threshold of a responding element is destined to rise as fatigue progresses. But in an all-or-none or isobolic mechanism the transition from the liminal to the subliminal state is not only critical; it is catastrophic. A range of uniform stimuli while it is, relatively speaking, traversing a progressively narrowing margin of efficacy will, in such a mechanism, still continue to arouse the quantal discharge. The threshold once passed, however, there can be but one result—elimination of the responding factor." In the course of time the element, which in this way has been eliminated, undergoes a lowering of threshold (recovery) and is once more provoked into activity. In a muscle mass in which a large number of fibres are undergoing rotational activity of this type a sudden cessation of stimulation will find individual fibres in all stages of fatigue and recovery. The flat "plateau" previous to cessation of stimulation represents a resultant of activity of the rotating constituents (Chapter IV). Immediately stimulation ceases, certain elements which would have been called into activity had stimulation continued fail to add their tensile stress, and others cease at the same time to continue their contraction. The result is that when stimulation ceases there is

almost immediately a gradual diminution of the "plateau." This leads to a more or less prolonged "nose" before the rapid portion of the curve of relaxation commences.

In passing it may be noted that a curve in which a sharp "angle" exists is an adequate guarantee of the absence of this rotational effect, for when gross asynchronism of activity of fibre units is present the "angle", for purely statistical reasons, must be rounded. This has been strikingly brought out in the case of reflex responses, such as the stretch reflex (*639*, *365*). However sudden the cessation of activity in this form of contraction, the commencement of mechanical relaxation is never abrupt.

THE SIGNIFICANCE OF THE CURVE OF RELAXATION

We have now to consider the nature of the curve of relaxation. What has been said in this regard of the twitch applies equally well to the tetanus. We have found in the former case that the curve of relaxation being concave upward suggests a passive process. The experiments on summation led us to conclude that contractile activity *per se* ceases at the "angle" and the curve of relaxation is in reality no more than the curve of a "viscous" body stretched by a decremental force; in this case the torsion-wire myograph. In the tetanus the same thing appears to be the case, but under ordinary circumstances it is difficult to analyze the first part of the curve owing to the great tendency toward asynchronous cessation of activity of the individual fibre units. In favourable records, that is, those in which the "nose" is slight, it has been found that the rate of the first half of relaxation is approximately constant, as indicated in table 9. The curves are probably susceptible of mathematical analysis, but since the coefficient of viscosity of a recently active muscle is not yet known, the significance of mathematical treatment would be problematical (see Chapter IX).

THE INFLUENCE OF THE CIRCULATION

Arresting the circulation quite naturally accelerates the onset of fatigue.[6] In figure 62*a* an optical record of the responses of an intact gastrocnemius is shown after stopping the circulation. It will be noted that the "plateau" slopes in these responses, which is characteristic of fatigue.

[6] An interesting study of the effect of cutting off the circulation on human muscles has recently been made by MacWilliam and Webster (*677*). They find that not only is the onset of fatigue very greatly hastened, but movement in the ischaemic limb is associated with severe pain and other subjective sensations. Attention may also be drawn to Bourguignon and Laugier's demonstration that diminished circulation to the muscles of dog and man greatly alter the characteristics of excitability (diminished chronaxie, and increased rheobase; Bourguignon, *137*, pp. 359–369; also *138*). Fatiguing by excessive stimulation leads to an augmentation of the chronaxie without affecting the rheobase (*609*).

Similar results may be obtained by tying the femoral artery. After ligation for a period of over 20 minutes, though there is some recovery, the "angle" of the twitch and tetanus has not, in my experience, ever regained its previous precision. It is evident, therefore, that these changes are accelerated by stopping the circulation. Six to ten hours after the cutting of the nerve (at 20°), even though the circulation remains active, the "angles" also disappear permanently, owing presumably to progressive nutritive changes of the muscle substance following upon nerve section. Such observations warn against the unrestricted acceptance of inferences as to the normal activity of muscle drawn from experiments performed upon excised tissue.

Another effect produced by diminishing or cutting off the circulation has already been alluded to, namely, the rapid decrease in the degree of tension developed at the height of tetanus. This is of interest in the light of Gruber's (*412, 418*) observation that raising the blood pressure in mammalian muscle (cat under urethane) quickly counteracts any existing fatigue, and whether fatigued or normal, it increases the total tension developed. Cannon and Nice (*186*) rightly attributed the "beneficial" effect of adrenaline on muscular contraction largely to increase in blood flow, but from the work of Gruber and Fellows (*419*), Gruber and Kretschmer (*420*), and Gruber (*413, 414, 415, 417*), it is evident that in addition to the circulatory effect adrenaline has a *direct* action in counteracting fatigue, for it "improves" contraction in excised muscle (cf. Guglielmetti, *426*). The direct effect of adrenaline has by Lange (*577*) and others been attributed to the power which it possesses par excellence of decreasing the permeability of muscle interfaces, in this way preventing oedema and imbibition of water by the fibre. In keeping with this Mme. Lapicque and Nattan-Larrier (*618*) have found that adrenaline *reduces* the chronaxie of a normal muscle and also of a muscle whose chronaxie has been abnormally increased by fatigue. Beattie and Milroy (*61*) have observed also that in minced muscle adrenaline diminishes the rate of "fluoride" synthesis of lactic and phosphoric acids (to a "precursor"). We shall see that these observations are of importance to an understanding of the function of the sympathetic nerve supply of skeletal muscle (Chapter XVI).

THE INFLUENCE OF TEMPERATURE UPON TETANIC RESPONSES OF INTACT MUSCLE

The effect of temperature upon tetanic responses of intact muscle has not yet been thoroughly studied with accurate technique, but preliminary experiments have yielded results which in many ways are very suggestive.

It will be recalled that our analyses of single responses (Chapter III) harmonized with the useful working hypothesis of Gasser and Hill (*390*), and have given added evidence in justification of the separation of muscular processes into (1) an active chemical phase, and (2) a passive or "viscous" phase. The curve of relaxation appears to be an expression of this latter period, while the duration of the response is in all probability controlled by underlying chemical activities. With these points in mind, let us now examine temperature effects upon short tetani.

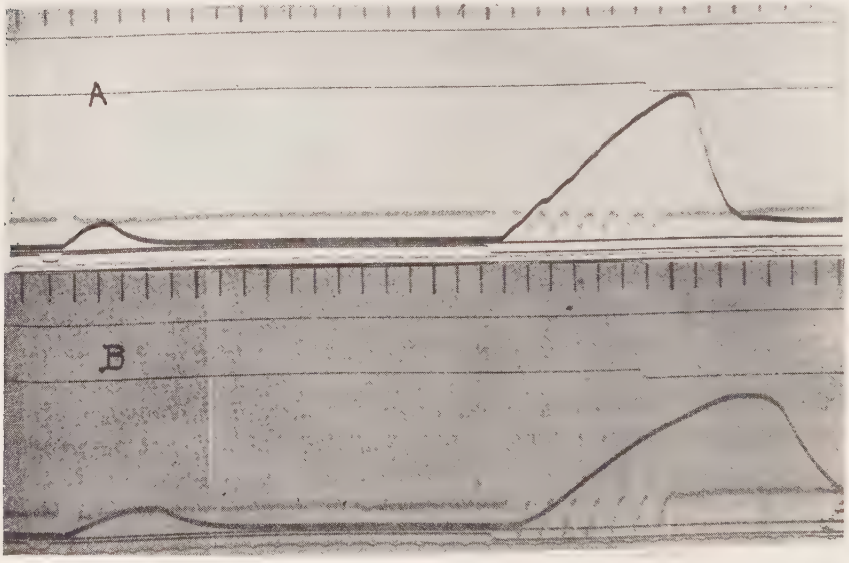


FIG. 63. Responses of an intact frog's gastrocnemius to a short tetanus of 7 stimuli at 50 per second preceded by a twitch. From above downward are: time signal indicating 0.02 second; "off" short-circuiting key causing cessation of the tetanus; galvanometer string; myograph; line indicating zero tension; short-circuiting key for the twitch and the beginning of tetanus; vibrator indicating the rhythm of stimuli.

A. Preparation at T 20°. The slope of the ascent in this figure is approximately 40 degrees with base line. Duration of terminal response, 42σ.

B. Same preparation two hours later at T 10°; slope of ascent 32 degrees; terminal response, 90σ.

In figure 63 records are given of short tetanic responses of the same gastrocnemius preparation (frog) at 20° (A) and at 10° (B) respectively. It is evident to inspection that the rate of ascent (*i.e.*, the slope of the rising tension) is not materially influenced by the change of temperature. At 20° the ascent in its steepest region forms an angle of 40° with the base

line. At 10° the angle is 32°. If one correct for the differing tension in the two,—to compare the maximal rate of the proportional rise (Hartree and Hill, *440*),—the temperature coefficient, as judged by the resulting corrected slope, is extremely small, *i.e.*, of the order of 1.2 to 1.3. As emphasized by Gasser and Hill (*390*) it is likely that the rate of tension increase (as well as that of relaxation) is determined by the internal resistances of the muscles; consequently this low value yields important confirmatory evidence in favour of their view.

With reference to the curve of relaxation, the presence or absence of a sharp subsidence "angle" enables us to distinguish between true "viscous" effects and the statistical result of inequalities in the duration of response of individual constituents. It will be seen in figure 63 B that the "angle"

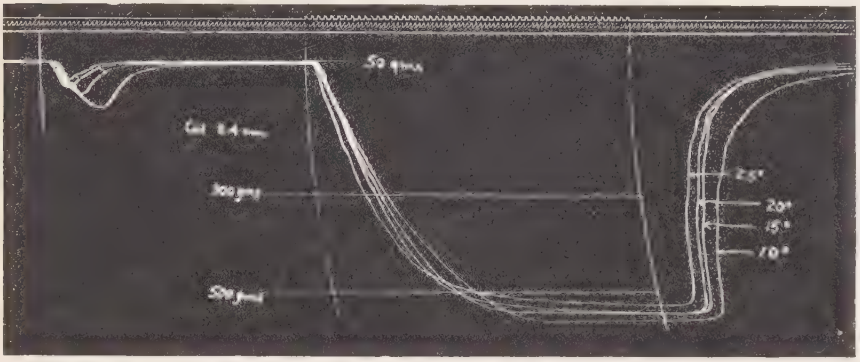


FIG. 64. Smoked-drum record of twitch and short tetanus of intact gastrocnemius at 10, 15, 20, and 25° respectively. Note the relatively small effect of temperature on the rates of ascent and relaxation. Initial tension 50 grams. Stimuli indicated by the top signal. Time in 0.01 second by the signal immediately beneath it. (*Proc. Physiol. Soc.*, *Journ. Physiol.*, vol. 58, p. xxxvi.)

is rounded at this temperature (10°), and consequently the rate of relaxation is little more than an index of the rate of cessation of activity of the individual fibres, and probably only in the region of approach to the base line can one measure true viscous effects. But even if we put these considerations aside (which is improper), the maximum rate of proportional fall as observed in figure 63 B is only 1.55 times slower than that in figure 63 A. These observations have been further substantiated in less accurate kymograph records shown in figures 64 and 65. It will be seen that the rate of rise of tension is practically unaltered by the temperature, and the same is true of the curves of relaxation. This is of particular interest in view of the fact that the method of kymographic recording permitted

extensive shortening, and consequently internal frictional effects could, under these circumstances operate more effectively than in the more nearly isometric optical responses. Satisfactory determinations of temperature coefficients, therefore, must take due consideration of the amount of shortening permitted during activity.

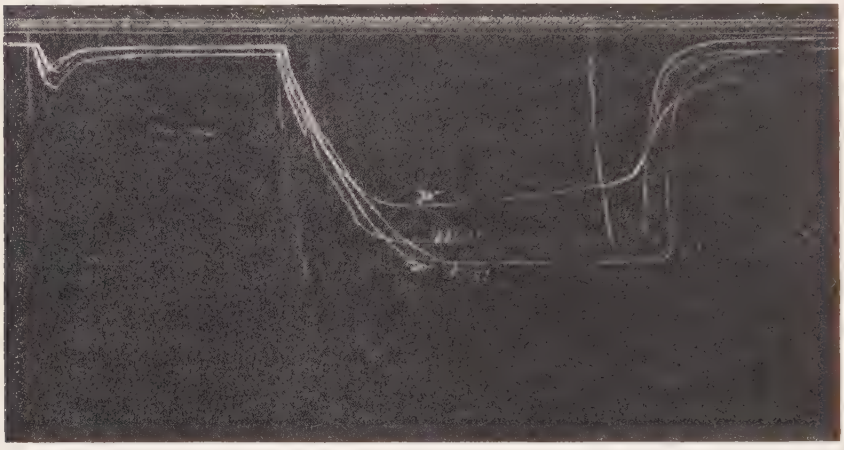


FIG. 65. Another preparation under conditions similar to those in figure 64 save that the initial tension is only 25 grams. Temperature varied from 15 to 30°. As will be seen in the response, a temperature of 30° is harmful to the muscle. It did not recover when the temperature was again lowered even though the circulation in the muscle was still active.

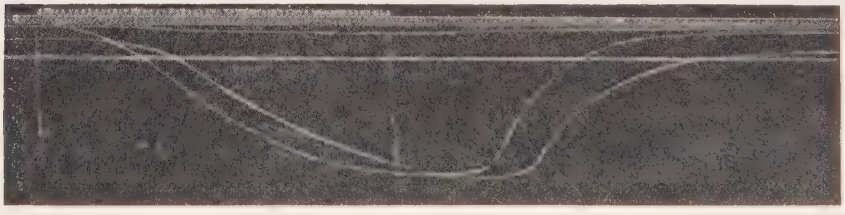


FIG. 66. The same preparation as that from which the responses in figure 64 were taken as 1 to 2°. Note the large increase in the duration of the terminal response with slight increase in the initial passive tension. This also shows the decrease in the tension developed at low temperatures.

I am aware that higher values for the rate of relaxation have been reported in the literature for the responses of excised muscle bathed in Ringer. I would urge that these high values do *not* give evidence of genuine temperature effects upon fundamental physiological processes, but are an ex-

pression of the rate of deterioration of the surviving tissue, together with the increasing degree of asynchronism which accompanies that process (cf., *e. g.*, *440*, *265*).

When we turn to the terminal mechanical response of a tetanus and examine the effect on it of temperature alterations, the picture is quite different. Here, as indicated in figure 63, the duration of the terminal response at 20° is 42σ and at 10° is 90σ, giving a Q_{10} well above 2. In the smoked-drum records the duration of this interval cannot be determined with accuracy owing to the absence of electrical responses as well as of an "angle;" but here too, the Q_{10} appears to be of the same order of magnitude.[7]

The observations, therefore, on the rate of ascent and the rate of relaxation, together with those on the duration of the terminal response, are in keeping with the analyses made upon the temperature coefficient of the twitch. As already indicated, they are most readily interpretable on the basis of the viscous-elastic body hypothesis of Gasser and Hill (*390*, *479a*).

SUMMARY

In this chapter are described the more important mechanical aspects of tetanic responses as recorded with an isometric myograph. The aim of studying the finer details of such responses is to obtain light upon the nature of the contractile process. The tension developed in a tetanic response rises to a maximum as the initial length of the muscle is increased and falls away again as the initial length is increased still further. In an intact muscle with active circulation it is usually difficult to demonstrate the maximum without severely damaging the tissue by initial stretching.

It is pointed out that the duration of the terminal mechanical response of a tetanus is an index of the concentration of the ions responsible for the maintenance of tension. Five important factors influence the duration of the terminal response. (*a*) The greater the initial length of a muscle the greater the duration of the terminal response. (*b*) The more nearly isometric the contraction the longer the terminal response. (*c*) The more prolonged the tetanus the greater the enhancement of the last response.

[7] In a preliminary note (*348*) these kymograph curves were analyzed, and the duration of the terminal response measured to half-relaxation was given. This yielded a value for the 10° interval of the order of 1.4. It will be seen that this method of analysis confounds two apparently separate processes, involving, as it does, the terminal response and the first half of relaxation. The value, though of interest in showing an algebraical summation of the temperature coefficient of two processes, cannot be regarded as significant for either alone.

(*d*) The higher the rate of stimulation within certain limits the greater the terminal response. (*e*) Lowering the temperature increases the response.

The tetanus is characterized by an "angle" similar to the "angle" of the twitch. All factors which tend to prolong the terminal response, save one, tend also to smother the "angle." This, on statistical grounds, is interpreted as due to an unequal liberation of acid among the individual muscle fibres, with the result that they do not cease activity simultaneously. In the case of shortening during contraction another cause of asynchronism is made effective, namely, the unequal amount of shortening among the individual constituents. This probably accounts for the apparent exception to the rule that all factors which tend to prolong the terminal response tend also to smother the "angle."

It is pointed out that the curve of relaxation being concave upward probably represents the "viscous" return of the muscle to its resting shape. The temperature coefficient (10°) of the rate of tension development in a tetanic response and of the rate of relaxation, is of the order of 1.2 to 1.3 while that of the duration of the terminal mechanical response is of the order of 2.0.

CHAPTER VI

The Innervation of Individual Muscle Fibres in Relation to Fatigue. The Problem of the Neuromuscular Junction

"The innervation of the striated musculature may be numbered amongst the many problems which have turned out to be far less simple than they appeared to be to an earlier generation of investigators. This is true whether we have regard to the structural or to the functional side of the problem" (Wilson, *1052*, p. 234). There are two important anatomical aspects of the question which demand consideration, both relating to the mode of innervation of individual muscle fibres. Does a single fibre ever receive two motor end-plates, and if it does, do they originate from the same segment or indeed from the system, *i.e.*, are both somatic, or is one of sympathetic origin? The latter problem will be considered in a later chapter on tonus. In the present chapter we propose to deal with the former question, especially in relation to the possibility of *plurisegmental* innervation of individual fibres. The evidence to be considered divides itself into two parts, namely, the anatomical evidence for plurisegmental innervation and the physiological evidence.

Anatomical evidence of plurisegmental innervation of individual fibres

It has long been known that whole muscles are usually supplied by more than one segmental nerve; in fact muscles which are unisegmental are rare. Though this was probably known as early as the time of Vesalius (*1000*), Panizza (*748*) and Kronenberg (*561*) appear to have been the first (1836) to demonstrate it by direct experiment. They observed that stimulation of either of the two roots (lumbar VIII or IX) supplying the hind limb of the frog caused well-marked contraction of the gastrocnemius muscle. The question of the anatomical distribution of segmental nerves in frog's muscle was not investigated until somewhat later. The early embryologists pointed out that many muscles represented the fusion of several embryonic myotomes and were thus polymeric in origin, but the embryological data are not clear cut (*1052*) so our evidence is to be drawn chiefly from the simple fact that a large majority of the muscles, *when fully developed*, are plurisegmental with reference to their nerve supply.

Sherrington (*873*) has pointed out that the more distal a muscle in a given appendage the more complete is the spatial fusion in the distribution of the individual segmental nerves. Thus in the rectus abdominis there is but slight overlapping in the distribution of the segmental nerves: paralysis of one nerve (*e.g.*, tenth thoracic of a monkey) causes practically complete paralysis of the area of rectus which it supplies. The same is true of the psoas, though here the line of division is somewhat less distinct. In the biceps and sartorius, on the other hand, the line of demarcation between the individual segmental nerves is not so well defined, though when the third lumbar root is stimulated the upper part of sartorius contracts most intensely while with fourth root stimulation the lower part contracts most markedly. Similarly with biceps (supplied by 6, 7, and 8). In the metacarpal or digital muscles the segmental distribution of the nerves appears to be entirely fused, since stimulation of any anterior root supplying these muscles produces a practically uniform contraction in all parts of the muscle. Our question, therefore, is to settle whether this fusion in distally placed muscles is the result of plurisegmental innervation of individual fibres or merely caused by intimate admixture of individual fibres receiving nerves from one or other of the two roots. Figure 67 gives a diagrammatical representation of these two possibilities.

Recently de Boer (*118*) has noted that in the gastrocnemius of the frog the spatial fusion in the distribution of roots VIII and IX is not complete, for when root VIII is stimulated—the tendon hanging free—the muscle becomes curved ventrally, while root IX tends to produce a curvature in the opposite direction. This shows that the fibres nearest the bone are supplied predominantly by the VIIIth root. This had been observed previously by Samojloff and Wassiljewa (*842*) in their third communication on plurisegmental innervation (December, 1925). Unlike de Boer, they fixed the muscle isometrically, passing a style horizontally through the belly of the muscle. When one root was stimulated, the point of the style went up while with the other it went down.

Krause (*556*) and Eckhard (*263*) searched carefully in the frog for individual fibres with a double motor end-plate and were unable to find convincing examples of such innervation. Kühne (*566*, *567*) made a similar exhaustive search and found a few rare instances of very long fibres possessing two end-plates, but no attempt was made to decide whether the two endings arose from different segments. It is well to remember in considering the anatomical problem of plurisegmental innervation that Floresco (*310*) and Cavalié (*191*) found several instances of individual motor nerve fibres which bifurcated and gave off terminal filaments to two or three

motor end-plates, in some cases on one and the same muscle fibre. Similar observations have recently been made by Garven (*385*) Boeke (*108*) and Hines-Loeb (*487a*).

The experiments of Agduhr (*20, 21*) have thrown further light upon the question. He has examined the flexor digitorum muscles of cats and rabbits, and has taken advantage of the fact that these muscles are supplied by the lower two cervical roots and the first thoracic. Using a modification of the Bielshowsky technique, he found it possible to discriminate between nerve fibres and end-plates at various periods of degeneration. He resected in a cat the first thoracic root ninety hours before the death of the animal, and the VIIth cervical root fifty-eight hours before death. This left the VIIIth cervical root unimpaired. On killing the animal after the period just indicated, the flexor sublimis digitorum muscle was examined and two of the groups of segmental nerves could be distinguished by their differing states of degeneration. The endings of the third group (the VIIIth cervical) were normal, and those of the first thoracic were distinguishable by their more advanced, and those of the VIIth cervical nerve by less advanced degeneration. By these criteria he believed it possible to show that individual fibres were often innervated by fibres from two successive segments. When first published these experiments received criticism on the basis of inadequate degeneration time, and in a subsequent contribution (*21*) Agduhr confirmed his previous conclusions by increasing the degeneration interval. His figures are convincing and the only possibility of error, as Garven (*385*) has pointed out, is that the accessory end-plate might have been sensory and not motor. His experiments would indeed have been more convincing if the anterior roots had alone been severed, in which case the sensory fibres would have remained intact. He pointed out, however, that all of his end-plates occupied a hypolemmal position which is strong evidence in favour of his interpretation. There would seem, therefore, no just ground for denying that in the flexors profundis, communis and sublimis digitorum of the cat and rabbit a certain proportion—but probably not a large proportion—of individual fibres *are* plurisegmentally innervated.

This question has recently (1925) been examined by Garven (*385*) in the panniculus carnosus of the hedgehog (the fascial muscle sheet corresponding to the platysma myoides of man). The innervation of this muscle sheet is such that segmental nerves do not converge before reaching the muscle, though there is considerable spatial overlapping in the peripheral distribution of the nerves of individual segments. Garven found occasional very long fibres in this muscle which had two end-plates, one at either end. He remarks that these were not numerous and were apparently never

present on short fibres. He says, however, (p. 412) "I was not successful in finding such a [short] fibre with a plurisegmental innervation, not, I think, because they do not exist, but on account of the very small number of these fibres which could be found and followed for any considerable distance." We have, therefore, in the panniculus carnosus another clear instance of a muscle possessing *some* fibres with plurisegmental innervation.

As far as one can determine from the literature no one has given adequate anatomical proof of the existence of plurisegmental innervation of the fibres in frog muscle. Kühne, as we have already mentioned, found a few rare instances of long fibres with a double end-plate, but these were not shown to arise from different segments. Kulchitsky (*569*) in his exhaustive investigation of a frog muscle, states emphatically that no individual fibres were observed to have two end-plates. He examined the gastrocnemius and the sartorius muscles. Consequently in view of Kühne's and Kulchitsky's painstaking search for double innervation, it is unlikely that plurisegmental innervation is extensive in the frog. Lindhard (*647*, p. 5) states that plurisegmental innervation of muscle fibres in the frog is common without giving evidence or authority.

PHYSIOLOGICAL EVIDENCE FOR PLURISEGMENTAL INNERVATION

We have already noted that both Panizza and Kronenberg elicited a response in the gastrocnemius muscle by stimulation of lumbar roots VIII or IX. This experiment was recognized and investigated in greater detail by Eckhard (*263*) and Peyer (*768*). Panizza and Kronenberg regarded the dual nature of the innervation of many muscles as a protection against fatigue, for they found that when one root had been stimulated to exhaustion responses could be elicited through the other root.[1] The more fundamental

[1] The circumstances which led Kronenberg (*561*) to write his prize essay of 1836 are of considerable historical interest. Panizza (*748*) had published his letter to Buffalini in 1834. This letter contained the remarkable observation that when one anterior root is cut or even when as much as two-thirds of the nerve plexus distributed to the muscles of one joint are cut away, the movements of the limb, though at first somewhat weaker, soon return apparently to their normal vigour. Panizza suggested that the innervation which would make possible such a recovery of function must result from the individual nerve roots having "a community of function." He suggested as a result of this that each motor filament of a limb plexus is capable of maintaining the motor function of the whole plexus and that the purpose of so large a number of roots is the assurance of alternative pathways in the event of injury. The limb plexus, in other words, is of physiological rather than anatomical significance (Sherrington). In Müller's *Text-Book of Physiology*, published also in 1834, we find the opposite opinion expressed, namely that the limb plexuses have rather an anatomical significance. In this he was supported by the experiments

question of investigating the tension development of the muscle when stimulated through each group singly and through the two simultaneously was examined in 1882 by Gad (*370*). He found (frog) that the sum of the tensions developed when the individual anterior roots were stimulated singly was approximately equal to that developed by the two roots when stimulated simultaneously. This, according to Gad, holds true both for single and tetanic stimuli, a conclusion confirmed some years later (1907) by Frölich (*345*). In 1884 Exner (*292*, *293*, *294*) examined the cricothyroid muscle of the rabbit and observed that when one of the two motor nerves[2] supplying this muscle (the superior laryngeal, and the medial laryngeal, (*294*) rabbit; (*649*) dog) are cut the muscle does not degenerate, and he suggested in view of this that the individual fibres of this muscle were doubly innervated. The possibility of sensory innervation was not at this early date taken into consideration. Lederer and Lemberger (*623*),

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of van Deen (1834) who had examined the question on the sacral plexus of a frog. He held that severing of any one nerve trunk caused certain specific muscles to become paralyzed (*230*). In 1834 we find the Berlin Faculty offering a prize for an original investigation into the structures and functions of nerve plexuses. The requirements were as follows: "Indagentur structura et virtutes plexuum nervorum; anatomica et microscopica observatione exquiratur, utrum fibrillae quae vocantur primitivae nervorum plexum brachialem, lumbalem sacralemve intrantes, in ipso plexu confluant, an sine vera earum anastomosi solummodo decussentur misceantur novo ut ordine prodeant; praeterea experimentis in animalibus frigidi calidive sanguinis instituendis evincatur, utrum irritatio in nervum, qui plexum intrat, agens per consensum in toto plexu et per nervos inde oriundos ad omnes musculos propagetur, an irritatio nervi intrantis per aliquas solum plexus partes in continuatas ejusdem nervi fibrillas singulosque musculos agat: unde natura plexuum nervosorum eorumque differentia ab anastomosibus vasorum dilucidetur." Sherrington points out that the subject must have been instigated by Müller himself. Kronenberg, being attracted by the question, set out to find the answer through a series of experiments on the cervical nerve roots of the rabbit. These he exposed and stimulated each one in succession. He concluded that excitation of any single root entering into the brachial plexus produces contraction of practically all the muscles of the limb. He urged also that if this be so, only a small part of the central organ would be fatigued in order to bring about sustained contraction or prolonged movement, since each root participated in bringing about the contraction of each muscle. The pattern for individual movements must therefore lie centrally and not in the anatomical distribution of the nerve. For further historical details concerning the later development of this interesting question, one is referred to Sherrington's paper entitled "Notes on the arrangement of motor fibres in the lumbo-sacral plexus" (*873*).

[2] Exner (*292*) was the first to establish that the cricothyroid of the rabbit and cat has a double motor nerve supply. The motor supply from the superior laryngeal was well known, but he described in addition a second motor branch from the pharyngeal plexus to which he gave the name *laryngeus medius*. This nerve was also found in the dog by Livon (*649*).

working in Doctor Exner's laboratory, carefully re-examined this muscle in 1907 with a Fick isometric lever. They found that the summed tensions developed in response to stimulation of each nerve separately was very little greater and often exactly the same (see their figures 4 and 5) as that developed by simultaneous stimulation of both nerves. The results of Lederer and Lemberger therefore supersede those of Exner, but they do

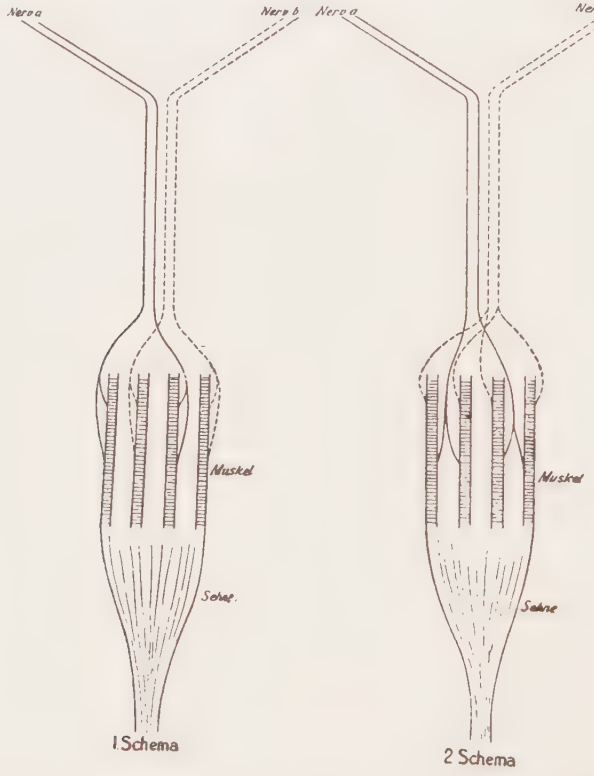

FIG. 67. Lederer and Lemberger's diagram of the two possibilities of segmental innervation of individual fibres. (*Pflüger's Arch.*, Bd. 119, p. 95, 1907.)

not explain his failure to obtain evidence of degeneration. Lederer and Lemberger's admirable diagram is reproduced in figure 67. It is possible that the presence or absence of degeneration is difficult to detect in a muscle as small as the cricothyroid. Lederer and Lemberger found, however, that the tension relations observed in the cricothyroid did not hold for the flexors sublimis, communis and profundis digitorum, for when these muscles were

examined by a Fick lever stimulation of single roots were usually quite as effective from the viewpoint of tension development as simultaneous stimulation of all the roots supplying it (see their figures 6 and 7). Agduhr finds, in accordance with Lederer and Lemberger and with his own morphological results, that the flexors sublimis and profundis digitorum develop almost as much tension when a single root is stimulated as when all three are stimulated simultaneously. From this he concludes that as many fibres are called into play by stimulation of a single segmental nerve as are brought into activity by stimulation of all three simultaneously. It is not clear from Agduhr's description that precautions necessary for adequate fixation and prevention of shortening were taken, and one cannot therefore estimate accurately from the tension relations how large a proportion of individual fibres are plurisegmentally innervated. As we shall see, the occurrence of shortening during a response materially alters the tension developed. When the shortening permitted is extensive this source of error becomes very important.

It would be misleading to apply experimental results obtained in the case of higher mammals to conditions of innervation obtaining in the frog, and, vice versa, failure to obtain evidence of plurisegmental innervation in a frog does not exclude the possibility of its occurrence in mammalian muscles. Moreover, because it is found in a given animal in a distal (digital) muscle does not indicate that it also exists in more proximal muscles. In the frog the problem has been attacked by a large number of investigators. Thus, Beritoff (*77*) reports that stimulation of root VIII or IX singly gives rise to only 15 to 20 per cent less tension than when roots VIII and IX are stimulated simultaneously. His method of recording permitted shortening of the muscle as a whole and this circumstance renders it necessary to make a correction of the observed tensions.[3] Katz (*542*) observed that the tensions of VIII plus IX singly is 41 per cent greater than that observed when both are stimulated together. Samojloff (*841*), on the other hand, who took precautions to prevent extensive shortening, obtained a value of 20 per cent and sometimes less. Samojloff (*839, 841*) also recorded the *electrical responses* of gastrocnemius muscle of a frog in response to stimulation of the separate roots and found that the summation of electrical effect was almost complete (fig. 68), *i.e.*, the height in millimeters of the action current produced by stimulation of root VIII was approximately half that produced when roots VIII and IX were stimulated together. This observation has been confirmed by de Boer (*119*) who obtained monophasic responses. Katz (*542*), moreover, has found that there is little if any overlapping in the heat production, *i.e.*, the heat liberated by roots *ab* when stimulated together

[3] This point has also been emphasized by Miss Boyd (Amer. Jour. Physiol., vol. 78, p. 254, Oct., 1926).

is approximately equal to the heat of $a + b$. de Boer (*117*) has also brought forward the interesting point that a veratrinized muscle (gastrocnemius) gives clear-cut evidence against the view of plurisegmental innervation. When a muscle poisoned with this alkaloid is rhythmically stimulated through its nerve until the "veratrin contraction" wears off, stimulation of the other root causes a typical veratrin curve, showing that in these fibres the veratrin effect had not yet "worn off." It might be urged that de Boer's results are to be explained on the basis of local action of veratrin at the end-plate, but one may reply to this that typical veratrin effects are to be obtained in a denervated muscle (*132*). Samojloff, de Boer, and Katz

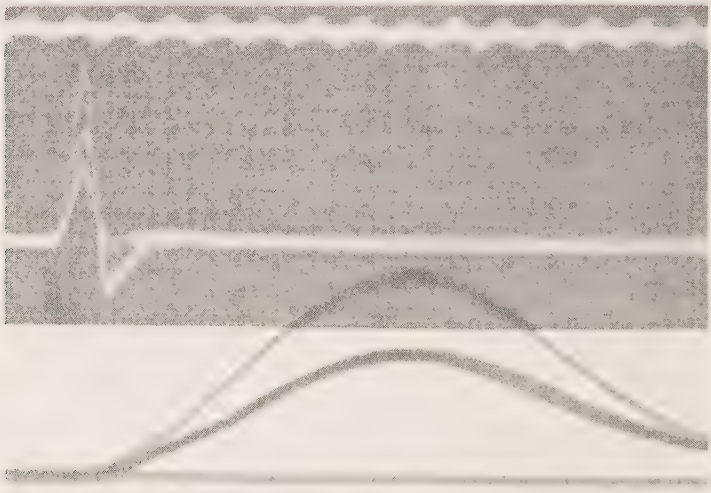

FIG. 68. One of Samojloff's simultaneous electrical and mechanical records obtained in root stimulation. The two small action currents were from the separate roots and the large one from the two roots stimulated together. (*Pflüger's Arch.*, Bd. 210, p. 121, 1925.)

conclude on the grounds of the foregoing observations that the gastrocnemius muscle fibres are not plurisegmentally innervated.

Samojloff has also given the following ingenious argument (*841*) in favour of monosegmental innervation (frog's gastrocnemius). If individual fibres of a muscle are innervated by nerves from two segments, stimulation of one root at a low rate (*e.g.*, 5 per second) should not much influence a previously fused isometric tetanus elicited at a high rate of stimulation from the other root. If, however, the low rate of stimulation under these circumstances should show itself by rhythmic increase in pre-existing plateau tension it gives evidence of new fibres being brought into play. When

subjected to experimental test, Samojloff found that the 5 per second stimuli applied to the second root did cause a rhythmic "notching" of the fused tetanus of the other root. The reverse experiment, namely, stimulating at a low rate by one root followed by stimulation through the other with a rapid faradization, did not obliterate the 5 per second rhythm. Taken together one could scarcely ask for a more convincing demonstration of monosegmental innervation.

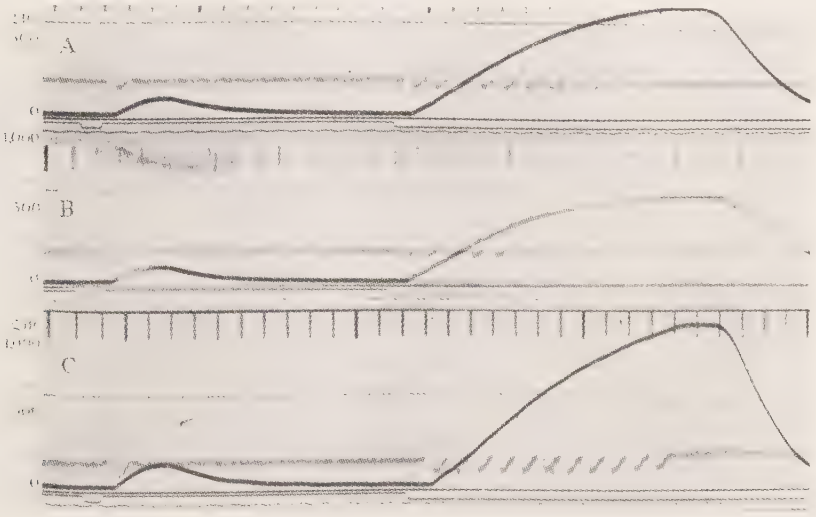

FIG. 69. Responses of the intact gastrocnemius stimulated through its lumbar roots. Temperature 16°; time above in 0.02 second. From above downwards are: "off" key; string of galvanometer; myograph; line of zero tension; "on" key; vibrator showing rate of stimulation.

A. Root VIII stimulated alone.

B. Root IX stimulated alone (doubly exposed).

C. Roots VIII and IX stimulated simultaneously.

Two-minute intervals were allowed between each response. Weight of frog 35 grams. Rate of stimulation 50 per second. The strength of stimulation was in each response 0.5 cm. coil distance above maximal, which, provided monophasic shocks (break) are used, does not appear to spread for more than 1 to 2 mm. down the nerve (*358*).

Experiments with torsion-wire myograph (*358*). Opportunity has been taken in the course of the present investigation to examine simultaneously the electrical and mechanical responses of gastrocnemius during root stimulation. Intact decerebrate frogs were used and the integrity of the circulation was insured. The isometric recording lever gave opportunity to examine the tension relations under conditions permitting relatively small

degrees of tendon shortening. It was found that when the VIIIth root of a 35-gram frog was stimulated at 50 per second for a short interval the tension developed in one experiment was 500 grams. The IXth root yielded 685 grams giving a total of 1185 grams for the two singly (see fig. 69). When stimulated simultaneously, 1060 grams were developed (table 10). There was, in other words, an overlapping of approximately 11 per cent and this extent of overlapping in the tension relations was approximately that observed in a large number of preparations; in a few it was considerably less. The question arises, therefore, as to whether this is to be considered

TABLE 10

Stimulation of lumbar roots VIII and IX in a 35 gm. frog (Rana temporaria). Summary of three experiments. Tetanus composed of break induction shocks at 50 per second

T = 15.0°; muscle (gastrocnemius) intact.

ROOT	TWITCH		TETANUS	
	Electrical response	Mechanical response	Electrical response	Mechanical response
	mm.	*gram*	*mm.*	*gram*
VIII	7.8	105	4.8	600
IX	7.7	100	5.8	465
	15.5	205	10.6	1065
IX and VIII	15.0	135	10.0	985
	TETANUS		TETANUS	
VIII	9.0	400	4.5	500
IX	13.0	610	5.0	685
	22.0	1010	9.5	1185
VIII and IX	20.0	900	8.9	1060

as evidence that a small per cent of the fibres in the gastrocnemius are innervated by fibres from both roots or whether the overlapping may conceivably have some other origin.

The electrical responses are consistent with Samojloff's observations (single twitches) in showing practically no overlapping. Occasionally the summed magnitude of the single action currents was 4 or 5 per cent greater than the maximal action current. This suggests that the higher percentage of mechanical overlapping may have its cause in the mechanical conditions of recording rather than in double innervation.

The influence of shortening in experiments on root stimulation. (See

also Chapter IV.) When allowed to shorten during a response, a muscle develops less tension than when it contracts under as nearly as possible perfect isometric conditions. In the experiments just described the amount of shortening at the tendon has been notably small, *e.g.*, 0.1 to 0.5 mm. Owing, however, to the diagonal disposition of the fibres the shortening of the individual elements may nevertheless be of considerable magnitude, and the resultant tension greatly diminished for purely mechanical reasons (Katz, *542*). Thus, figure 80 (Ch. VII) shows that if the extent of shortening occurring during a short tetanus is altered from 0.4 to 0.8 mm., the

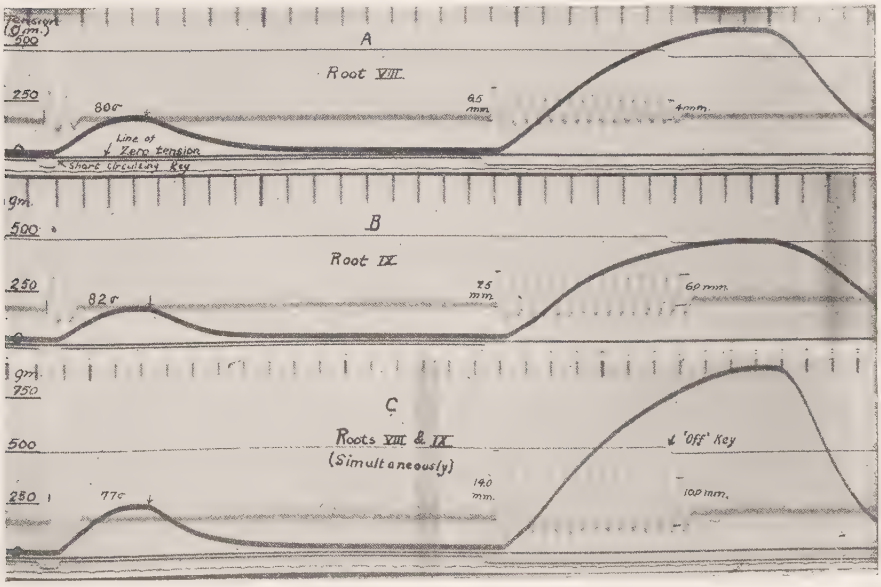

FIG. 70. The same preparation as figure 69, but stimulated at 100 per second instead of at 50. First responses double. The summation of electrical responses is particularly clear in this record (*361*).

total tension developed may be decreased by 25 to 30 per cent. Consequently, when a single root is stimulated the individual fibres shorten less than when the muscle executes a maximal response, *i.e.*, when the fibres of root A are assisted by the fellow fibres in root B. When a single root is stimulated, therefore, the individual fibres develop individually and collectively more tension than when both roots are stimulated simultaneously. One of the signs of an alteration in the degree of shortening is a change in the duration of the response. Consequently, if in root stimulation we can find evidence of an altered duration of individual responses, we shall have

direct evidence that there are altered tension relations of the individval fibres. Such evidence, in fact, is not wanting. In figure 69, A and B, the duration of the terminal mechanical response measured to half relaxation was 320σ and 290σ, while in C, in which both roots were stimulated simultaneously the duration was 270σ. In the latter instance, therefore, the individual fibres had shortened more and had developed less tension fibre for fibre than in A and B in which the single roots had been stimulated. This factor has been shown to be of sufficient consequence to account for the 10 to 15 per cent overlapping in the tension developed between single and double root stimulation, and it is therefore not necessary on experimental grounds to assume that a large proportion of individual fibres are innervated by motor nerves from both segments (see also fig. 70). It may be noted that this conclusion is in complete accord with the anatomical observations upon gastrocnemius of the frog.

Concurrent stimulation of the two roots. If root A is stimulated and during the tetanus plateau which results, root B is stimulated for a brief interval, there follows an immediate increase of the tension already developed by A. An experimental difficulty has been encountered in obtaining synchronous stimulation of the two roots, and this has resulted in the action currents of the two independent sets of stimuli being out of phase with each other and they are consequently unsatisfactory for purposes of comparison. The mechanical responses, however, are invariably clear-cut (fig. 71). This again indicates that a large proportion of *fresh* fibres are called into play when root B is stimulated.

Another feature which has been brought out in these experiments is the influence of muscle shortening, however slight this may be. We shall see in the next chapter that when a muscle under appreciable initial passive tension shortens in a tetanic response, the successive action currents diminish in size *pari passu* with the muscle length. In the experiments on concurrent stimulation of the two roots precisely the opposite effect has been observed, *i.e.*, that during lengthening of a muscle, as when it relaxes from the concurrent stimulation of B, the electrical responses are of progressively *increasing magnitude*. This will be referred to again in the next chapter.

It may be noted also that a muscle can maintain greater tension than it can attain. Thus, after the response of root B in figure 71, the myograph falls, but not to the previous plateau level; having been *assisted* by the fibres of root B, the fibres of A can remain more shortened and at a higher tension than they had previously developed. In keeping with this the successive electrical responses in A are smaller after stimulation of B than

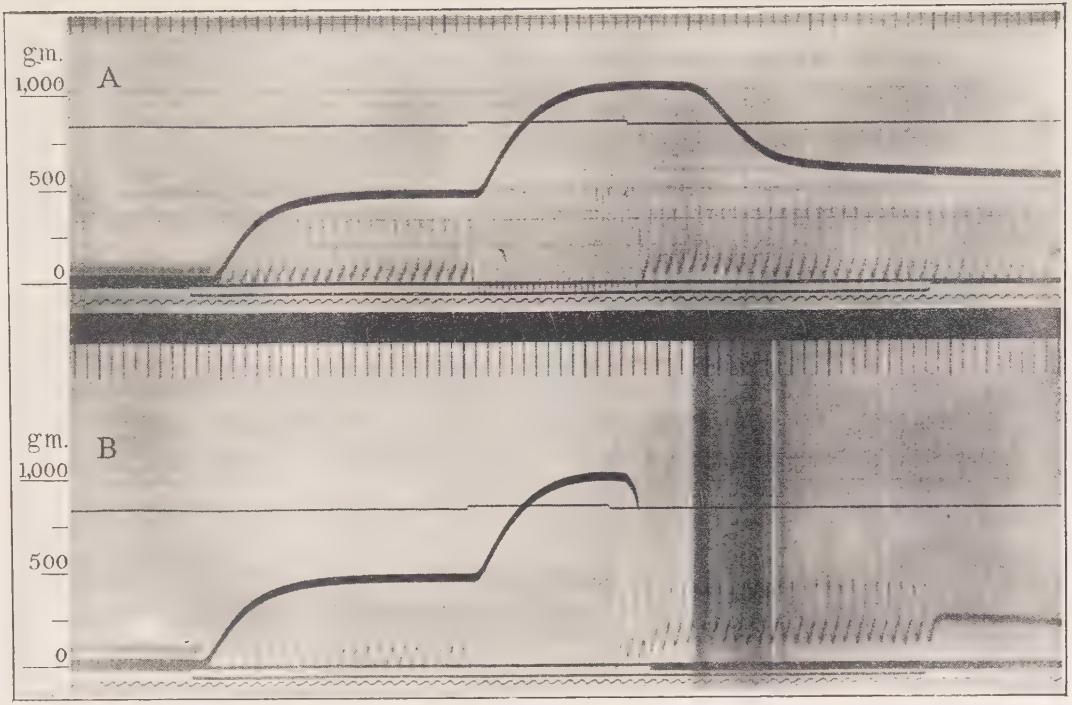

FIG. 71. A record of an unsuccessful experiment in which the VIIIth root was stimulated continuously and the IXth for only a short interval indicated by the upper signal. During the interval in which both roots were being stimulated the mercury key used to separate make from break shocks failed to separate owing to the primary of the two coils being connected in series. Inasmuch, however, as doubling the rate of stimulation during the plateau of a completely fused tetanus does not materially increase the tension already attained, the increase of tension in this response is clearly to be attributed to the recruitment of added muscle units. This is also borne out by the increased amplitude of the electrical responses despite the fact that their rate is doubled. In the lower response the tendon broke at the height of tetanus.

Note in A the increasing size of the electrical responses during the relaxation (*i.e.*, lengthening) from the second stimulation. This shows that the electrical responses increase when the fibre is caused to lengthen. In B after the tension has broken, note the small size of the electrical responses. Here the muscle is presumably at its shortest length (*358*).

before. This gives clear indication that the electrical response *varies with the length of the muscle and not with the tension which it has developed.*

THE DIFFUSIBILITY OF FATIGUE PRODUCTS

Sherrington (*873;* p. 711 and 753) raised the question of whether fatiguing a muscle by excessive stimulation of one root influences the response obtained by stimulation of the other root. The whole problem of plurisegmental innervation turns upon the solution of this question. All authors are agreed that after fatiguing to complete inexcitability through one root the muscle responds vigorously when stimulated through the other root, but until recently there has been no available evidence as to whether the response elicited through the second root did or did not show the effect of the stimulus applied to its fellow root. There are two possible ways of interpreting this experimental result: (1) new fibres are called into play by the stimulation of the second root and provided fatigue products do not diffuse from the previously activated fibres there would be no signs of fatigue. (2) It may be urged, as have Cattell and Stiles and Beritoff, that the local excitation fatigue occurs in the region of entry of the motor nerve. According to this view, when fatigue has abolished the response of root A, stimulation of root B is effectual because it enters the same fibres through different end-plates.

Sherrington (*873*) pointed out that obliteration of the circulation caused an apparent diffusion of fatigue products from active to inactive fibres, at least the response of root B was less vigorous after root A has been fatigued in the absence of the circulation than if it were fatigued in an intact preparation. In his words, "When instituted on an excised muscle the degree to which fatigue produced from the 'fatiguing' root influences the response obtainable from the test root is more marked, the influence becomes apparent earlier and persists longer (p. 711)." This conclusion has been generally confirmed by recent investigations.

Thus, Samojloff (*839*) in a series of experiments fatigued the muscle by stimulating one lumbar root, A; after this he stimulated the other root, B, until it was also fatigued. He then stimulated intermittently the first root, A, and found that it had apparently recovered. Samojloff concluded quite logically from this result that the majority of fibres in gastrocnemius must be innervated by only one root and that the fatigue products of one fibre do not readily diffuse into neighbouring fibres. Samojloff, however, used excised preparations, while de Boer (*117*) performed the same experiment on intact muscle (of a spinal frog) and reached the same result. Neither author, however, compared the results, as did Sherrington, before and after

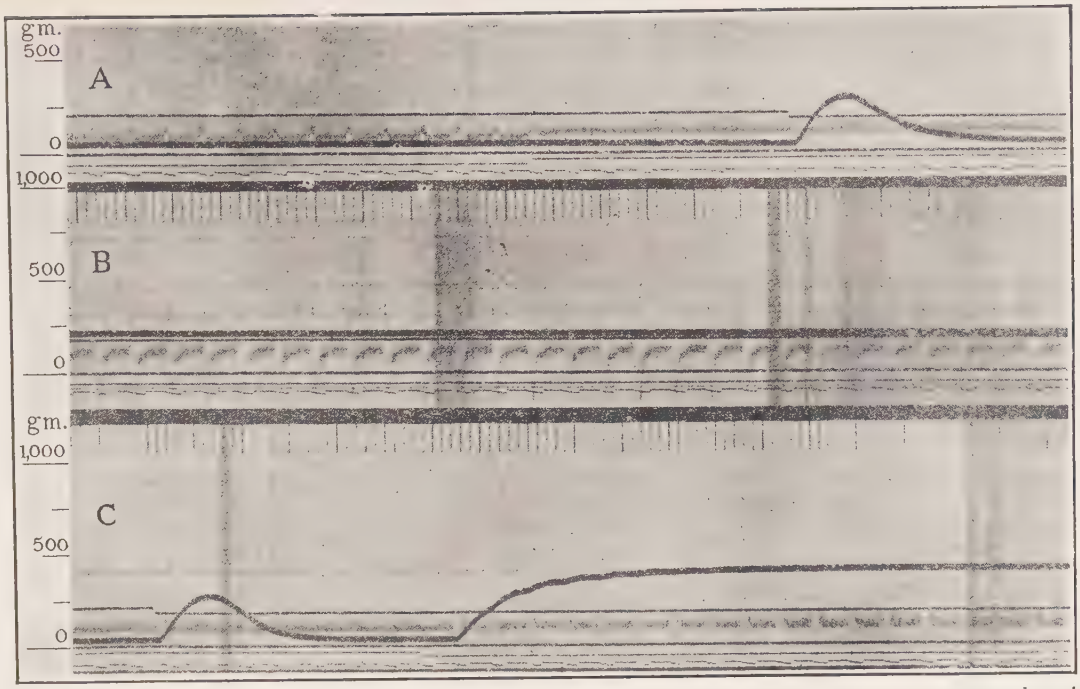

FIG. 72. Responses of the intact gastrocnemius stimulated through its lumbar roots showing that one root may be stimulated to exhaustion without greatly affecting the response from the other root.

C. Root IX was stimulated by a single break shock shown by the signal. This is followed by the beginning of a tetanizing stimulus at 28 per second applied to the VIIIth root.

B. A "sample" of the responses during the exhaustion of the VIIIth root taken 55 seconds after the end of the last record.

A. A continuation 2 minutes later of the same tetanus after the mechanical response had fallen to a negligible value. This tetanus is ended about half-way down the plate, after which there is very slight relaxation and then another break shock is delivered to the IXth root. It will be seen that the "angle" in this second twitch is if anything more precise than that in C. The relaxation, however, is slightly less rapid (*358*).

removal of the circulation. It may be mentioned, however, that neither of these experiments exclude the possibility that a small proportion of fibres are plurisegmentally innervated; but they *do prove that the majority are not so innervated* and they give fair indication that the acid metabolites of a fatigued fibre do not readily diffuse into an adjacent unfatigued fibre.

Similar evidence was obtained in the course of the present investigation. Advantage was taken of the "angle" of the twitch as an indication of fatigue. A twitch of root A was recorded and immediately root B was fatigued to complete exhaustion, and once more a twitch from root A was recorded. It was found that the "angle" of the second twitch, after complete fatigue of the fibres innervated by the fellow root had occurred, was indistinguishable in an intact preparation from the "angle" preceding the fatigue of root B. Such a record is shown in figure 72. In the lower record (C) root A was stimulated by a single break-shock, and immediately after this root B was tetanized. The first part of the tetanic response is shown and a later "sample" of the response after an interval of 55 second is given in the middle record. The gradual diminution of the mechanical response in this record is noteworthy. After a two-minute interval the fibres innervated by root B were practically exhausted and the final record (A) shows the termination of the tetanization of B followed by another twitch from root A. It will be seen that the second "angle" is if anything sharper than the first. In this preparation a distinct hyperpnoea followed a few minutes after cessation of the tetanization. This of course provides a satisfactory control of integrity of the circulation. The same experiment was performed on excised sciatic gastrocnemius preparation, and invariably the "angle" of root A after tetanization was less precise than that previous to the tetanization of root B. In other words, as Sherrington first pointed out, fatigue products do tend to diffuse from one fibre to the next in the absence of the circulation. In view of the cutting of the vaso-motor nerves necessary to such an experiment on an intact animal, it is almost surprising that the resulting tendency toward œdema should not cause a breaking down of the inter-fibre barriers. When the circulation is cut off completely, it is probably something in this nature,—an altered permeability of some peripheral membrane around the fibre,—that leads to the diffusion of the acid metabolites. The fatigue products, of course, are readily diffusible through the capillary walls into the blood stream, the presence of lactates in the blood (*367*, *486*, *487*) following severe exercise giving clear evidence of this.

The demonstration of the non-duffusibility of the fatigue products in normal muscle is of importance in accounting for the relative unfatiguability of postural reactions. We shall find in later chapters that prolonged con-

tractions, such as are involved in a stretch reflex, are made possible through the rotational activity of individual constituents, and from minute to minute, though an equal number of fibres may be performing all-or-none contractions, they are not necessarily the same fibres, for they appear to change from moment to moment, according to the particular afferent organ which the stretch stimulus happens to excite. There is, in other words, a shifting of the incidence of stretch among the individual afferent organs, and this causes a shifting or "rotation" of the muscle fibre responses.

Redfield and Edsall (*799*) have recently made important observations upon heart muscle during fatigue. If the ventricle of a tortoise is placed in an oxygen-free atmosphere and caused to respond at regular intervals the amplitude of contraction decreases logarithmically to complete extinction, and these authors have discovered that the amount of lactic acid present in the muscle increases *pari passu* with the degree of fatigue. In other words, the capacity for developing tension in the heart varies inversely with the amount of lactic acid (or lactate) free within the muscle. They emphasize, however, that the duration of the contraction does not increase in the heart muscle as it does in skeletal muscle when fatigued. The area of each contraction is, in other words, a constant fraction of the original "tension-time" diagram. This striking demonstration of the reciprocal relation existing between lactic acid and tension development is fundamental to any theory of fatigue.

The absence of increased duration of contraction when fatigued might conceivably be accounted for by the inevitable asynchronous character of cardiac fibre responses, but this appears unlikely, for Redfield and Medearis (*800*) observed the same phenomenon in the isolated strips of auricle.

The first careful analysis of the process of fatigue in muscle was made by Ranke (*790*). When a muscle is kept under continuous stimulation it soon loses its excitability and fails to contract, however strong the stimulus may be made. Under such circumstances irreparable damage probably occurs in the muscle. Nevertheless, if allowed to remain quiescent, more or less restoration occurs. Ranke suggested that metabolites liberated within the muscle are responsible for this inhibition of contractile power. He observed that extract of fatigued muscle of one frog when injected into the circulation of another brought on fatigue in the second animal. Control experiments with unfatigued muscle failed to give this result. This general result has been confirmed by many observers (see especially Lee, *625*). The recent developments in muscle physiology make it likely that the most important of the metabolites responsible for fatigue is lactic acid, or more specifically the hydrogen ion of lactic acid.

This leads us to a consideration of the nature of the motor end-place and the mechanism of transmission of stimuli from nerve to muscle.

THE NEUROMUSCULAR JUNCTION

The problem of how a nerve excites a muscle aroused the curiosity of the earliest investigators (cf. du Bois-Reymond, *123*, ii, pp. 698–735). Many explanations have been suggested, but the one which has figured most prominently in recent physiological discussions is the belief that intermediate between the nerve and the muscle there exists a third tissue of unknown anatomical characteristics which serves to transmit the nerve impulse to the muscle. This belief had its origin in the experiments of Claude Bernard (1850). He, in association with T. J. P. Pelouze (*762*) pointed out that the Indian arrow-poison, curare, blocks transmission from nerve to muscle but does not destroy the activity of either (cf. also von Kölliker, *553*, 1862), and in view of this, the suggestion was made by Kühne (*562*, *563*) and Pollitzer (*775*) that curare acts upon a hypothetical substance intermediate between the nerve and the muscle. They found that after a curare block the "neural" portion of the fibre was still more excitable than the non-neural. Further historical details are to be found in Langley's (*584*) Croonian lecture.

In Chapter II certain factors influencing the end-plate delay have been described, and on the basis of the low temperature coefficient, together with the known attenuated morphological condition of the terminal portion of motor nerves (*102*), it was suggested that the delay is largely due to slowing of conduction in these terminal regions. One cannot, however, urge unqualified acceptance of this inference without consideration of other possible explanations. It may be urged, for instance, that the classic experiments of Waller (*1013*) on the so-called fatigue of the end-plate are out of harmony with such an assumption, especially in view of the ample confirmation and extension of these experiments by Abelous (*1*) (Cf. Ioteyko *512*, *513*).

Fatigue within the individual fibre.[4] Waller, as is well known, found that after a muscle had been rendered inexcitable by excessive stimulation of the nerve, it would still contract when stimulated directly. From this it was inferred that fatigue occurs more extensively in the local region of the end-plate than in the individual fibre. A similar conclusion has been reached on other grounds by Cattell and Stiles (*190*). Now the majority of the experimental observations on plurisegmental innervation discussed in the present chapter,—except possibly the veratrin experiments of de Boer,—might conceivably be explained by the assumption of junctional fatigue, as opposed to muscle fibre fatigue. The assumption of junctionl fatigue

[4] A detailed discussion of the early literature relating to this problem is given by Ioteyko (*512*).

rests, as Beritoff (78) has recently insisted, upon the inference that metabolites tend to accumulate locally in the region of the end-plate. Consequently, a muscle which has been stimulated to exhaustion through its nerve should give a more or less unaltered response when stimulated directly (or when stimulated through accessory end-plates, which amounts to the same thing). Actually, however, a muscle so fatigued shows a greatly modified response when stimulated directly; in fact, a single twitch

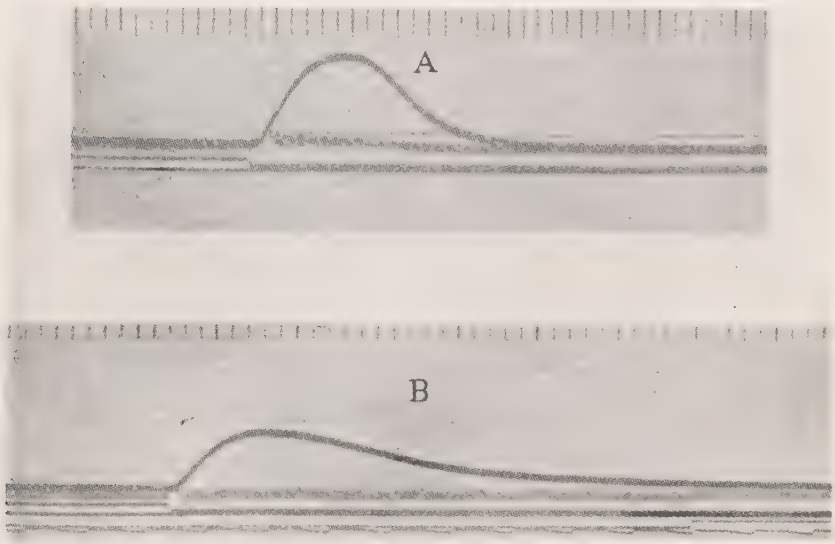

FIG. 73. The response of the same muscle before (A) and after (B) severe fatigue. In the upper response the muscle was fresh. It was then tetanized until it ceased to respond to nerve stimulation, and then stimulated directly. Such a direct response is shown in the lower record (B). The escape of the stimulating current is in the same direction to the action current. The periodic movement of the string in B is due to escape from the tetanizing stimuli still being applied to the nerve.

recorded immediately after a muscle has been completely fatigued through its nerve may be five times longer in duration than the twitch of the muscle when unfatigued, and only one-half to one-quarter as much tension may be developed; in other words, *the muscle as a whole has been affected*. One is justified, therefore, in concluding that the fatigue process is not wholly confined to the motor end-plate (cf. Beritoff and Iaschwili, *78*, *81*). A record obtained in such an experiment is shown in figure 73. In A, the muscle is stimulated before fatiguing through the nerve, and in B the muscle is stimulated directly during the termination of the fatiguing stimuli. The

escape of current will be seen in the galvanometer string, together with very minute superimposed action currents.

Other evidence which harmonizes with this conclusion is to be found in the Lapicques' (*609*) examination of the excitatory characteristics of normal and fatigued muscle. They observe, as explained in Chapter I, that normally a muscle fibre has the same chronaxie as its nerve; after stimulation through the nerve becomes ineffective owing to fatigue, the chronaxie of the muscle substance has usually doubled or trebled its resting value, *without* an alteration of its threshold (rheobase). Other evidence pointing in the same direction is to be observed in the ordinary fatigue curves of the text-books, which show progressive modification in the response of the muscle as a whole. This evidence is, however, indirect because such a modification might be the result of changes occurring at the end-plate, but since it is found that the same progressive changes occur when tested by direct stimuli, it is evident that the muscle as a whole is involved. Finally, the progressive modification of the "angle" with fatigue, described in Chapters III and V, is also in keeping with this general result, indicating that some fibres are more affected than others (leading to asynchronism). It is evident, therefore, that while after severe fatigue the blocking of the conduction occurs *at the motor end-plate*, the reason for its occurrence there is probably to be explained along the lines set forth by the Lapicques, namely, that acid metabolites have accumulated within the fibre as a whole, and have in this way altered the chronaxie of the muscle. It may be noted in passing that the accumulation of acid in the fibres leads to a concomitant diminution in size (but with an increase of duration) of the action current (Chapter VIII); associated with this there occurs also a slowing of the rate of conduction, in addition to the increase of the chronaxie just mentioned (see also, *341*).

The "local excitation" fatigue, which occurs when a muscle is stimulated directly (*1013*, *190*, *784*, *78*, *81*) for a more or less prolonged period, is probably to be explained by two contributing factors. (1) The *generalized* increase in the chronaxie of the fibre as a whole, due to metabolites. This gives rise to a condition which, in the absence of chronaxie determinations, is referred to somewhat loosely as a "rise in threshold." It may be mentioned again that, while the chronaxie becomes increased, the threshold for a constant current, *i.e.*, the rheobase, does *not* usually rise as fatigue progresses. The "threshold" for a faradic stimulus of course does rise, but this is due to its brief duration. (2) Electrolysis beneath the cathode. As an example of this, we may note that when the region of the motor cortex beneath the stimulating electrode is examined in experiments on cortical localization, it has been found recently (1925) that bubbles of gas are evolved beneath the tip of the electrode (Florey, *311*, p. 52). Similar effects undoubtedly occur when a muscle is stimulated directly, even though less intense stimuli are used. This would of course serve to raise the threshold locally.

The hypothesis of receptive substances. The precise way in which an impulse is transferred from the motor nerve ending to the muscle fibre still remains a matter of conjecture. The belief of the Lapicques has been set forth in the first chapter. Briefly, they look upon the action current of the nerve as the exciting stimulus of the muscle. In view of the fact that the time to maximum of the action current in nerve varies closely with its chronaxie, and the fact that normally the chronaxie of muscle approaches that of its motor nerve, the duration (and potential) of the action current

FIG. 74. Intraprotoplasmic ending of a nerve fibre within the ciliary body of the human eye. Note the indentation in the side of the nucleus. (Boeke, *Brain*, vol. 47, p. 7, 1921).

of the nerve is looked upon as sufficient to excite the muscle directly without the intermediation of a junctional tissue. Lapicque and others point out, moreover, that the discontinuities in strength-duration curves, which Lucas put forward as evidence for a junctional tissue, is unsatisfactory because these discontinuities have not been found in intact muscle stimulated with electrodes of small area (see Chapter I, fig. 23). Are we therefore justified in dismissing as improbable, in the case of skeletal muscle, the conception of specialized receptive substances?

Before discussing this question it would be well to remind ourselves of the anatomical details concerning end-plates.

Intramuscular terminations of motor nerves were studied by the earliest histologists and most notable were the contributions of Valentin (1836, *995*), Kühne (1862, *565*),

von Kölliker (1862, *553*), and Engelmann (1863, *279*) who made a systematic study of the end-plates in a large number of animals. They established among other things that the motor nerve terminates in an expanded end beneath the sarcolemma of the muscle fibre. With the development of histological technique the finer structural details of the end-plates were subsequently rendered visible. An important investigation was carried out by Huber and DeWitt (*502*) 1897, who also drew attention (as had Kühne and Engelmann) to the collection of nuclei in the region of the motor nerve termination. These were termed "end-plate" or "sole" nuclei. They are confined within a granular cytoplasmic material ("granular sole" or "end-plate" sarcoplasm) which Huber and DeWitt regard as an accumulation of sarcoplasma of the muscle. They remark also that the "nuclei of the sole are in structure very similar to the muscle nuclei, and we have regarded them

FIG. 75. A section in profile of the motor end-plate from a young mouse showing the reticular structure of the (fixed) "neuro-fibrils" existing within the granular sole. Boeke's "periterminal" net-work, believed to be identical with Langley's receptive substance, is not shown in this figure. (Boeke, *Brain*, vol. 44, p. 1, 1921.)

as such" (*502*, p. 179). They noted in addition that "in sections giving a surface view of the muscle fibres of the frog, double stained in methylene and alum carmine, it may be seen that the muscle nuclei are more numerous in that portion of the muscle fibre receiving the ramified endings of the motor nerve. Many of these nuclei are found in the thin layer of sarcoplasm in which the axis-cylinder branches terminate. These nuclei are comparable to the so-called sole nuclei, which, it will be remembered, were also regarded as nuclei of the sarcoplasma—muscle nuclei." The belief that the end-plate nuclei migrate from within the muscle fibre has more recently been supported by embryological studies (*976*). The association of motor nerve ending with the nuclei of the tissue which it innervates cannot be regarded as purely a matter of chance, for it is observed in tissues other than skeletal muscle. Thus, Wiggers (*1045*, p. 50) has noted that the nerve fibres enter the sinoauricular node of the heart "from above and divide into delicate plexuses from which

FIG. 76. Tiegs's drawing of end-plates showing the relation which he believes to exist between the transverse (*helicoid*?) striations and the end-plate nuclei. Figure on left from frog; that on the right from the leg muscle of the insect, *Scutigera*. *Trans. Roy. Soc. So., Australia*, vol. 47, p. 142.)

varicose fibres *terminate in simple or complex fashion around the nuclei of the muscle cells.*" And the fibrils of the auriculo-ventricular bundle frequently end about the nuclei of the ventricular muscle fibres (Wiggers). In a contribution by Boeke (*110*) on the morphological basis of Langley's receptive substance, he notes, "Here [smooth muscle] too the terminal nerve-fibres pass into the cell, ending within the protoplasm with loop-like expansions, which often are seen lying so close to the nucleus of the muscle cell that they make an indentation and thus are found lying in a shallow cavity in the side or on the top of the elongated nucleus, thereby proving their intraprotoplasmic position" (fig. 74). He believes, however, that morphologically the receptive substance of a muscle is to be identified with a "periterminal" network which he has observed between the motor ending and the interior of the fibre. The motor endings in his experience show hypolemmal neuro-fibrils which form a reticulum over the sarcoplasm of the "sole" (fig. 75), and from this reticulum there extends *into the myofibrillae* of the fibre the "periterminal" net, which he identifies with the junctional tissue. Boeke also finds evidence of the existence of "periterminal" networks in certain afferent endings (*e.g.*, Grandry corpuscles). The evidence for the identification of the "periterminal" net with junctional tissue is drawn from corresponding degeneration-times of the two after section of the motor nerves.

Another recent investigator makes the following observation: "In the endings of different nerves on striated muscle fibres of the frog I have observed a curious feature to which attention has not, so far as I am aware, hitherto been drawn. If a partial side view of the end-plate nuclei is obtained there can generally be seen protruding from the lower part of each nucleus a minute process. I cannot say whether it is the termination of one of the minute fibrils of the nerve ending, which sometimes appear to enter the nuclei, or whether it is a process formed directly from the nucleus. But of its existence there can be no doubt, and such a process is always found to lie in close connection, not with the muscle 'striation,' but with Krause's membrane. Even ordinary muscle nuclei can, in side view, be clearly seen to have a direct connection with Krause's membrane. This is clearly shown in figure 76 taken from the leg muscles of a Myriapod *Scutigera*. The nuclei, here, occur along the central axis of the fibre; and each nucleus is seen to be connected by short processes with Krause's membrane. The example is taken, it should be noticed, from a contracted region of the fibre; there has occurred an accumulation of dark material around Krause's membrane, which is thus hidden from view" (*980*, p. 147).

In 1921 I raised the question of the significance of the end-plate nuclei (*347*), and suggested that they might be associated in some way with junctional transmission. It had long been known that the nuclei of nerve cells supply to the cytoplasm a chromatic material, generally referred to as Nissl substance, and that this material disappears during activity (*241*, *242*, *243*, *245*). It was believed that the end-plate nuclei might similarly supply a ("receptive") substance concerned in the functional activity of the end-plate. Such a view might presuppose an excitatory process similar in kind to that occurring centrally, *i.e.*, without refractory period (Chapter XIV), but there is little evidence that such a process exists peripherally. Moreover, the evidence drawn from the staining results of "novocaine-brown" is, as Laugier and Legendre (*622*) courteously pointed out, open to the alternative explanation that the curare-effect

produced by novocaine, and by its coloured derivative, is due simply to an alteration in the time-relations between the nerve and muscle (heterochronism). This being a more likely explanation of the action of novocaine than that originally suggested by me, it is evident that the belief in a nuclear receptive substance is, on physiological grounds, not yet well substantiated. The morphological fact noted above, of the accumulation of nuclei in the region of the end-plate, cannot, however, be dismissed lightly. This is especially true in the light of Tiegs's and Boeke's observations. However, if one puts aside the evidence from "novocaine-brown," the function of the end-plate nuclei still remains a mystery.

There remains the important body of evidence adduced by Langley and others in favour of the existence of a junctional tissue. It is based upon the reactions of muscle to certain drugs such as nicotine, physostigmine and curare. When applied locally to a muscle in the region of the incoming nerve, nicotine, in a concentration which is inactive in the non-neural portion of the muscle, will readily cause prolonged twitching. The drug, therefore, is more active in the neural regions of the muscle than in the non-neural, and from this Langley (*584*, *585*, *587*, *588*) suggested that it acts upon some as yet unknown tissue within the region of the end-plate which, for want of knowledge as to its intimate nature, was termed "receptive substance." It was pointed out that the assumption of such a substance was amply justified by the activity of the sympathomimetic and parasympathomimetic drugs. These substances, in the majority of instances, continue to be physiologically active after the post-ganglionic fibres have degenerated (*585*, *589*). Langley (*587*) showed the same phenomenon to be true in the case of skeletal muscle, *i.e.*, that nicotine was more active in what before degeneration was the neural region of the muscle than in the non-neural.

It is, however, not unreasonable to suggest a "mechanical" explanation for Langley's findings, namely, that, since in the region of the end-plate the protecting hypolemma is thin or absent, a drug applied to this region has more ready access to the fibre. It is perhaps difficult to explain degeneration experiments on that ground, but one must note that the greater local effect of nicotine on what previously was the end-plate region is less marked with the lapse of time, and it is therefore possible that the sarcolemma gradually grows over the end-plate after degeneration is complete. Indeed, this is supported by morphological findings (*21*).

Moreover, such drugs as veratrin, caffein, and curare have a well-marked *general* effect upon muscle fibres, as Hartree and Hill (*441a*, *443*) and Lapicque (*608*) emphasized. This strengthens the view that the "localized" effects are due to differential facility of access. It is similarly arguable that the

sympathomimetic drugs, *e.g.*, adrenalin, act upon the general metabolism of the effector cell, as is evidently the case in the action of adrenalin on skeletal muscle (see Chapters V and XVI), rather than upon some focal point or "receptive" element.

Though it is perhaps not yet justifiable to stress too emphatically the importance of these objections to the conventional belief in receptive substances, it nevertheless indicates that their existence is not proved, and consequently that the simplest working hypothesis to account for neuromuscular transmission (*e.g.*, that of Lapicque, which postulates direct excitation of muscle by nerve) is probably the safest.

SUMMARY

The problem of the segmental distribution of motor nerves to muscles, and to the constituent fibres of muscles, has been considered in the light both of anatomical and physiological evidence. It is pointed out that the amount of spatial overlapping in peripheral distribution of nerves from any one segment with those from another segment, becomes increasingly extensive in the more distal muscles of bodily appendages, being least noticeable in the rectus abdominis and most marked in the flexors digitorum sublimis and communis muscles, where spatial fusion of nerves from several segments is almost complete.

In the frog there is no adequate anatomical evidence for the occurrence of individual skeletal muscle fibres innervated by nerves from different segments. A few rare instances were recorded by Kühne, but Kulchitsky failed to find any even as a rare anomaly. In the flexors digitorum of mammals (Agduhr, *21*) and in the panniculus carnosus of the hedgehog (Garven, *385*), on the other hand, plurisegmentally innervated muscle fibres are not uncommon, but no information is available as to the relative proportion between mono- and plurisegmentally innervated fibres. There are reasons for believing that the proportion is not large.

The physiological evidence for plurisegmentally innervated fibres is of three kinds. A muscle having a double or triple root supply is stimulated first by one root and then by the other, and the physiological disturbance is compared quantitatively with that elicited when the two (or three) roots are stimulated simultaneously. Observations on electrical and thermal responses offer no support in the gastrocnemius of the frog for the belief in plurisegmental innervation. Records of tension, on the other hand, are less clear-cut, but the divergent results obtained in the past have been shown to be due in large measure to the shortening which occurred during con-

traction, and due also to the diagonal arrangements of the fibres in gastrocnemius, the muscle commonly used.

It has been demonstrated that, provided the circulation remains intact, fatiguing to exhaustion of one group of fibres in a muscle does not lead to fatigue of a commingled group. It is inferred from this that individual fibres of a healthy muscle are protected from metabolites which accumulate in adjacent fibres. This is of importance in view of the fact that in long-maintained postural responses rotation of fibre activity undoubtedly occurs.

The nature of the motor end-plate is discussed, and the conclusion reached that in the present state of knowledge we are as yet unjustified in assuming the existence of a specialized ("myoneural"), junctional tissue possessing properties different from those of either nerve or muscle themselves. It is pointed out that the Lapicque-Lillie conception, which maintains that the potential difference of the action current of nerves is the adequate stimulus for the muscle, appears at present to be the safest and most conservative working hypothesis. Some at least of the alleged drug effects (*e.g.*, curare) are due not to localized action at the nerve endings but to effects on the muscle as a whole.

CHAPTER VII

The Electrical Responses of Skeletal Muscle During Repetitive Stimulation (Tetani)

Mechanical responses of muscle undergo characteristic alterations when the conditions under which contraction occurs are varied (Chapter V). We may now discuss the corresponding alterations in the *electrical* responses when contractions are executed under different mechanical conditions. The electrical response of the twitch of gastrocnemius tends to increase as the initial tension of a muscle is raised (Chapter III), but one cannot decide on the basis of this observation alone whether the change in electrical response is caused fortuitously, as, for example, by alteration of the distance between the leading-off electrodes, or whether it represents a physiological alteration in the response of each individual unit of the muscle.

Alterations in magnitude of electrical responses of a given tissue may be due to any one of several causes. (1) Variations in size may be produced by variation in physical conditions: (*a*) by alteration in distance between the leads, as when the muscle shortens; (*b*) by shifting of the leads on the surface of the tissue; (*c*) by alteration in the electrical resistance of the physiological tissue (as by drying) without alteration of the distance between the leads; (*d*) by alterations in the sensitivity of the recording instrument, such as a tightening of the string of the galvanometer due to heating. (2) Alteration in size of the electrical responses of the whole muscle may be produced by a change in the direction of the fibre constituents in a muscle with reference to the leads, which is equivalent to an alteration in electrical axis (Chapter I,) or direction of spread of excitation from fibre to fibre. Thus, in a pennate fibred muscle, the fibres may tend, owing to contraction, to become more diagonally disposed under the leads and in this way produce an apparent modification of the electrical record (*331*). (3) Alterations may occur owing to the addition of more fibre units. Watts (*1032*), for instance, has shown that the size in millimeters of the electrical response increases to a maximum *pari passu* with the strength of stimulus (sartorius). The tension developed increases similarly until a maximum is reached, which Watts quite logically interprets, according to the all-or-none principle as the point at which all the fibres are participating in the response. (4) The size of the electrical responses may be altered by fatigue. (5) Finally, alterations may be due to changes in the response of each individual fibre. We may accordingly ask ourselves whether changes in the electrical response of an individual muscle fibre ever does occur, and if so, under what circumstances.

Characteristic changes are to be observed in the size of the electrical responses during short tetani. The influence of the nature of the "leads" (*i.e.*, whether diphasic or monophasic) has been considered in Chapter I. In the experiments about to be described an

attempt has been made to render the responses as nearly monophasic as possible without causing tissue destruction. But as it has been found consistently that the alterations in magnitude of the responses occur to approximately the same extent in both monophasic and diphasic leads, when records are obtained under otherwise similar conditions, the fact that the responses are not completely monophasic does not vitiate the observations. In order to analyze the changes in the electrical response it is necessary so to control experimental conditions as to be able to consider the various possible causes of alteration separately.

1. Let us consider first the purely mechanical factors. The possibility of gross alterations in distance between the leads has been eliminated by obtaining responses under isometric conditions (Sherrington torsion-wire lever). Shifting of contact of the leading-off electrodes has been prevented by the use of the silver chloride pin, which, when inserted into the muscle substance, does not shift and is free of friction. There is an optimal distance of 15 to 20 mm. between the leading-off electrodes which ensures that the size of the electrical responses shall be at a maximum. Further separation does not change the size of the response, and consequently if the leads are always more than 20 mm. apart small alterations in the distance between them, such as occur when muscles shorten (± 1 mm.), will not in itself give rise to alterations in the size of the action currents. This precaution has always been observed. By keeping the muscle under approximately constant conditions of moisture and blood circulation, the resistance between the electrodes has been shown to remain approximately constant. Finally, changes in the sensitivity of the instrument, owing to heating, has been carefully controlled by frequent observation with calibrating currents.

2. Alteration in the direction of the fibre constituents as a possible cause of electrical alteration is more difficult to control experimentally, and consequently it is best to choose for experimental purposes a parallel fibred muscle in which all of the fibres extend throughout the length of the muscle. When such a muscle is examined electrically the disposition of the fibres with reference to the leads cannot be greatly altered. Sartorius is one of the few muscles which is parallel and has long fibres,[1] but it was found desirable in the majority of experiments to use other muscles because of the difficulty in fixating sartorius in the intact animal (Chapter III). Inasmuch, however, as the results obtained with sartorius were identical with those obtained with the gastrocnemius and other muscles, it is reasonable to conclude that the observations made upon gastrocnemius were not vitiated by the possibility of alteration in the direction of the fibres with reference to the leads. Moreover, when precautions are taken to prevent extensive shortening, the possibility of error from this cause, even in gastrocnemius, would be but slight. The arrangement of the fibres in the gastrocnemius of a frog, early investigated by du Bois Reymond (*123*), has recently been studied by Beritoff (*84*). A diagram of the fibres of gastrocnemius taken from his work is reproduced in figure 77.

[1] Even in sartorius, a classical parallel-fibred muscle, the fibres, as Mayeda (*696*, p. 143) has shown, do not extend throughout the entire length, for in a sartorius 25 mm. in length the longest fibres were in his experience only 20 mm. in length. At either end short fibres were to be found which dovetailed in with the longer fibres. The majority of fibres in sartorius, according to Mayeda, are only 70 to 80 per cent as long as the total length of the muscle. Consequently, even in sartorius it is possible that the two leading-off electrodes shall not be on the same fibre, and in this way modify the characteristics of the electrical responses (Adrian, *13*).

3. Alteration in the number of units stimulated can readily be avoided by using stimuli which are well over-maximal. A series of break-shocks from the separation key described in the Appendix are monophasic, easily made maximal, and have been proved equable by galvanometer records. Variation in the number of nerve units stimulated is therefore readily excluded. Extensive variation in the number of muscular units responding, such as might take place if lapsing and rotation (Pratt) of elements occurred during short tetani, is ruled out by the presence of a sharp "angle" in the mechanical record (Chapter V). Another source of error might arise, when using repetitive stimuli, if one does not allow sufficient time for recovery of the individual fibres between each successive stimulus. We know, however, that the end of the (relative) refractory phase of a muscle at 20° occurs not later than 4 or 5σ (*665*) after the stimulus. Consequently, stimulating at 100 per second should give ample time for recovery between each successive stimulus. In the present experiments a rate of 50 per second has been regularly used (an interval of 20σ between each response), which is much more than that necessary for complete recovery.

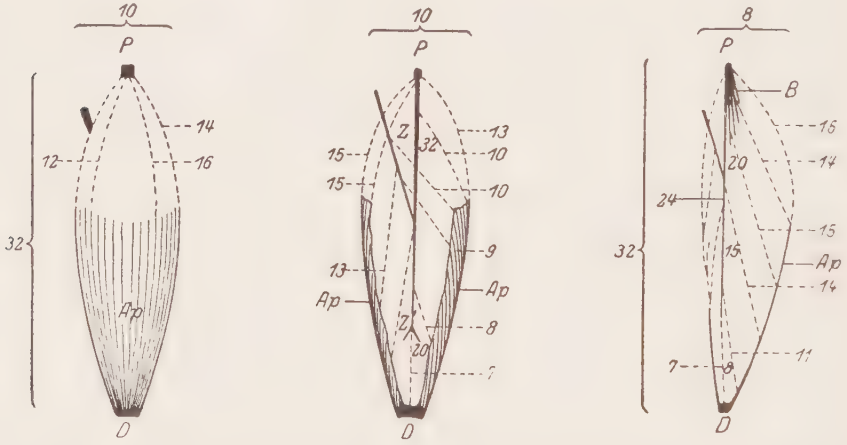

FIG. 77. Beritoff's diagrams showing the fibrillar arrangement of the gastrocnemius muscle of the frog. Numerals gives fibre length (mm.). (*Pflügers Arch.*, Bd. 209, p. 763, 1925.)

4. It might be argued, however, that in a short tetanus metabolites would accumulate within the muscle fibre ("fatigue") and in that way indirectly alter the magnitude of the response. To avoid this possibility experiments have been performed such as those described in Chapter IV in which each successive stimulus fell at, or approximately at, the "angle" of the mechanical response. This prevents accumulation of ions within the muscle. Inasmuch as the results obtained have been confirmed at all rates varying from 12 to 120 per second, one cannot assume that error has arisen either from inadequate recovery time or from accumulation of fatigue products within the muscle.

With these sources of error excluded there can remain but one explanation for the observed alterations in the size of the electrical responses, namely,

that they are physiological alterations in the response of each separate fibre within the muscle. The historical aspects of the question will be detailed in the next chapter. We will now describe the nature of the alterations which are to be observed in the electrical responses of short tetani.

DIMINUTION IN SIZE OF SUCCESSIVE ACTION CURRENTS DURING THE MECHANICAL ASCENT

Responses obtained with the torsion-wire lever. When, under appreciable initial passive tension, the intact gastrocnemius recording "isometrically"[2] is stimulated through its nerve by a short tetanus at 50 per second, the successive action currents, at first large, progressively decrease in size during the ascent, and become of constant size during the mechanical "plateau" of the response. Two such tetani commencing at different initial passive tensions of the muscle are shown in figure 78. It will be seen that the size, *i.e.*, the galvanometric amplitude, of the electrical response of the twitch, which precedes the tetanus, is in each case the same as that of the *first* response in the tetanus: at 57 grams initial stretch these action currents are 19 mm. in amplitude, and at 110 grams, 20 mm. During the *mechanical ascent* of the tetanus the "size" of the successive electrical responses diminishes continuously until the plateau is reached; they then become regular and are about half the size of the first galvanometric response. In some tetani (as in fig. 78 B) there is also a progressive slight diminution in the electrical responses during the plateau, but this is not common, and is usually associated with a gradually climbing mechanical "plateau." It will be observed that the size of the electrical responses maintained during the plateau is larger with greater initial tensions in approximately the same degree as is that of the first response. In table 11 are summarized the results of the experiment from which the two observations in figure 78 are taken. The parallelism between the electrical responses and tension developed is worthy of note. This harmonizes with the observation of Schenk (1896) that the successive electrical responses during a tetanus becomes greater as the tension of the tetanus plateau is increased.

In another experiment with the string somewhat looser (63 m. per ampere) the diminution in size of the successive electrical responses was particularly striking during the ascent of a tetanus which was composed of 29 stimuli, the first 12 occurring during the ascent. The size of these 12 were

[2] The actual shortening which occurred in these responses was of the order of 0.1 to 0.5 mm. "Isometric" as used in this monograph refers to a method of recording—*i.e.*, the torsion-wire lever, rather than a condition of contraction.

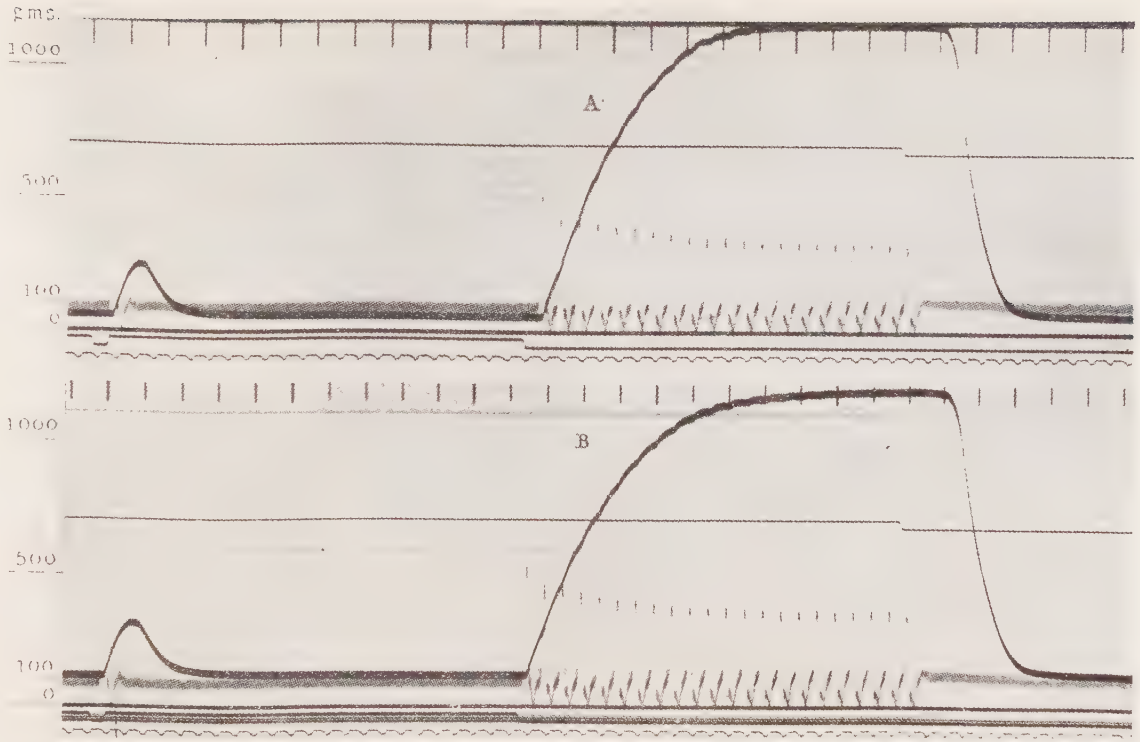

FIG. 78. Two responses of the intact gastrocnemius muscle of a 30-gram frog at 23.5°, each consisting of a short tetanus (of 22 impulses at 50 per second) preceded by a twitch. Time above signal = 0.04 second; short-circuiting key open for 0.02 second to let one impulse pass for the twitch and permanently open for the tetanus; the "wiggler" at the bottom shows the rhythm of the stimulus. At the left side mechanical tension is indicated. String tension 55 m. per ampere, at a magnification of 285. Stimuli, a series of break induction shocks of a coreless coil delivered by a Sherrington tortion-wire key (*323*).

A. Initial tension upon the muscle, 57 grams; tension developed above initial, 1,084 grams. Note fall in size of electrical responses during the ascent.

B. Same. Initial tension, 110 grams; tension developed above initial (tetanus) 1,094 grams.

respectively: 35, 31, 29, 28, 26.5, 25, 24, 23.5, 22.5, 21.5, and 21 mm. The remaining 17 plateau responses were each exactly 21 mm. in amplitude. The initial tension in this experiment (at 17°) was 40 grams and the plateau tension 1,560 grams, the highest tension yet developed in my experience by the gastrocnemius of a frog, being equal to 40 times its own weight (37 grams). The tendon broke during the next response and the experiment was discontinued.

TABLE 11

Showing the relation between the tension developed and the size of the electrical response in the twitch and tetanus of the gastrocnemius of a 30-gram frog

(For other conditions see legend of fig. 78)

INITIAL TENSION	TENSION DEVELOPED ABOVE INITIAL		SIZE OF ELECTRICAL RESPONSES			RATIO: ELECTRICAL RESPONSES
	Twitch	Tetanus.	Twitch	1st response of tetanus	Plateau responses	PLATEAU/FIRST RESPONSE OF TETANUS
			At 19°			
grams	*grams*	*grams*	*mm.*	*mm.*	*mm.*	
5–10	113	972	21.5	21.5	10.5	0.48
45	173	1125	23.0	23.0	13.0	0.56
110	181	1067	24.5	23.5	14.0	0.59
175	170	953	24.0	24.0	15.0	0.62
			Same preparation at 23.5°			
5–10	113	680	17.0	16.5	8.5?	0.41
34	150	1023	18.5	18.5	9.5	0.48
57	187	1084	19.0	19.0	10.0	0.52
110	198	1094	20.0	20.0	10.5	0.53
172	186	983	20.5	20.0	11.0	0.55
218	178	872	20.0	19.5	12.0	0.61
25	165	1025	16.0	16.3*	8.5	0.51

For other details concerning the twitch and the tetanus (duration, terminal response, etc.) in this experiment see tables 4 (Chapter III) and 9 (Chapter V).

* Showing that the string had tightened somewhat during the experiment (from 55 m. per ampere to 50).

Successive diminution of the electrical responses during the mechanical ascent has been observed in the responses of mammalian muscle as well as in frogs. In figure 79 are reproduced tetanic responses obtained in Fulton and Liddell's experiments (unpublished) upon the intact rectus of a cat stimulated through its cut (anterior crural) nerve.

The influence of shortening during contraction. At constant initial tension the greater the degree of freedom for shortening, as table 12 will show, the greater is the diminution of the successive electrical responses during the ascent, and the less the tension developed. Thus when but 0.05 mm. shortening is permitted (as measured by movement of the tendon) by

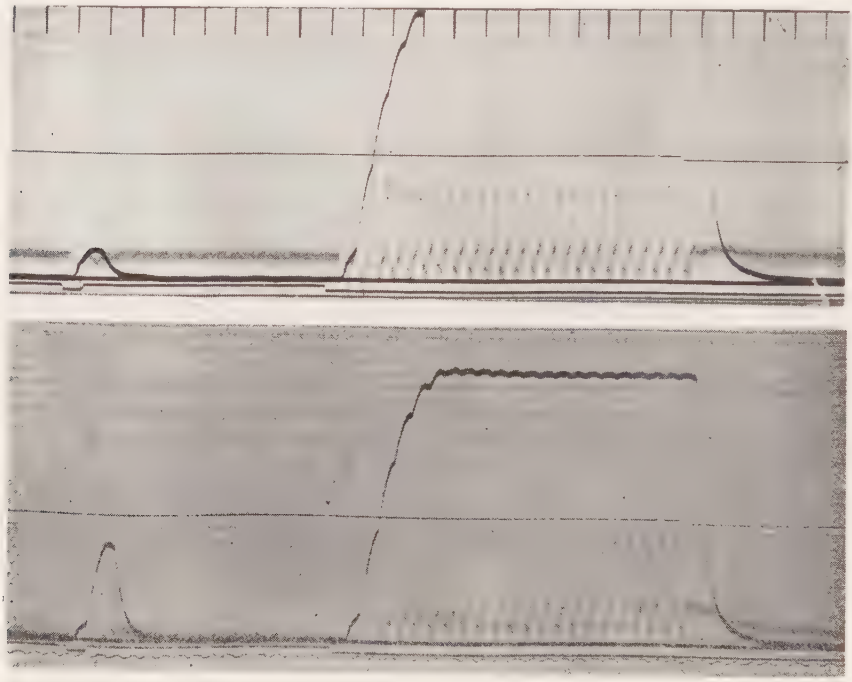

FIG. 79. The responses of the rectus muscle of a decerebrate cat to single stimulus (in the lower one it is double) followed by a short tetanus at 50 per second. Just before this response was taken the rectus muscle had been dissected away from its fellow muscles in quadriceps and freed as far as possible from all surrounding fascia. The "angle" of the twitch in the upper record is well marked and the successive diminution of the electrical responses during the mechanical ascent may also be noted. In the lower record there was a small amount of electrode movement during the response. The very short interval between the electrical and mechanical shortening in mammalian muscle may be seen to advantage in the upper record (A) in the second response of the tetanus. It is about 2.7σ (see Chapter II). Time above 0.04 second; myograph frequency 460 per second.

connecting the muscle with the myograph at a point very near (3.8 mm.) its axis, the tension developed in one experiment was 710 grams, and the ratio between the size of the plateau responses and the first response was 0.72, while with 1.03 mm. shortening (the muscle being attached 17.7 mm.

from the axis of the myograph) the tension developed was 543 grams and the ratio between the last and first electrical response 0.54. In another experiment, records from which are shown in figure 80, the ratios between the plateau and first responses varied between 0.73 and 0.52. By connecting the tendon at high initial tension in such a way as to prevent any shortening the ratio was increased in several experiments to 0.92. It appears from this that it is virtually impossible completely to prevent diminution in size of the successive electrical responses in gastrocnemius.

The effect on a tetanus of two responses of varying the degree of shortening occurring during activity is shown in figure 81.

TABLE 12

Showing the effect of varying degrees of shortening at constant initial tension (50 grams) upon the electrical responses, the tension developed and upon the duration of the terminal mechanical response of short tetani

The responses from which the lower group of measurements were made are shown in figure 80 (gastrocnemius muscle; 25-gram frog; $T = 14°$; string tension 50 m. per ampere in first; 55 in the second).

SHORTENING PERMITTED	TENSION	ELECTRICAL RESPONSES			DURATION OF TERMINAL RESPONSE
		First response	Last plateau response.	Ratio	
mm.	*grams*	*mm.*	*mm.*		
0.06	840	17.7	13.0	0.73	140σ
0.55	800	17.8	10.5	0.60	100σ
1.30	760	17.8	9.2	0.52	90σ
0.05	710	25	18	0.72	155σ
0.45	595	25	15.5	0.62	120σ
1.03	543	24.5	13.0	0.54	95σ

In view of the facts brought forward by Forbes, Ray and Hopkins' (1923, *331*) experiments, it may be urged, despite the very limited degree of shortening permitted, that the decline in size of the successive electrical responses during the ascent of gastrocnemius is caused by the fibres as they shorten becoming more diagonally disposed with reference to the leads. This, as Forbes and his co-workers have suggested, might cause the action currents of adjacent muscle fibres to interfere one with another. Experiments were accordingly made upon the sartorius, a parallel-fibred muscle to which, therefore, this objection would not apply. With sartorius as with gastrocnemius, there is an unmistakable decline in size of the successive electrical responses during the ascent (fig. 83 A), but the extent of the diminution in sartorius

for the same amount of shortening is less. Figure 82 shows two records of sartorius at different initial tensions (see footnote on page 218). The plateau electrical responses are 1.5 mm. greater in the response at the higher (*i.e.*, in A) initial tension than at the lower, and there is a large difference in the electrical responses of the two twitches (10.5 and 15.5 mm.).

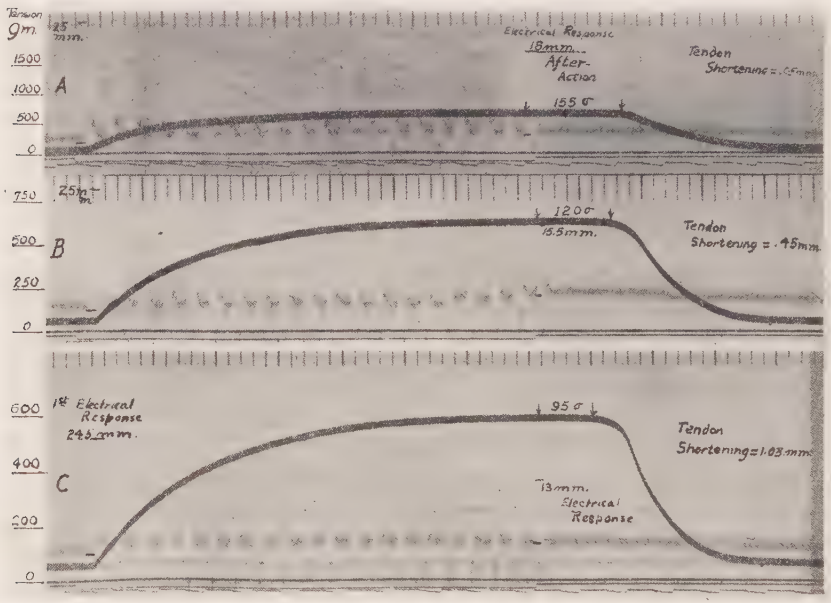

FIG. 80. Three tetanic responses of an intact gastrocnemius of 25-gram "winter" frog in which the amount of shortening occurring during the response has been varied. In A the shortening (0.05 mm.) was the least, etc. The responses of this record have been analyzed in the lower rows of table 12. It will be seen that where the least shortening occurs during the response there is the least diminution in size of the successive action currents and also the longest duration of terminal mechanical response (indicated on the figure by arrows). The size of the first electrical response of the tetanus is nearly the same in all three cases, which ensures the constancy of the initial conditions (length, etc.) in the three records. Time above = 0.02 second. String tension 8 mm. per millivolt in all three records. Below line of zero tension is the short-circuiting signal controlling stimulating electrodes (*361*).

Like gastrocnemius, the smaller the degree of shortening permitted in sartorius, the less the diminution in the successive action currents. A number of responses were recorded in which there was no diminution at all. In these no shortening was permitted and the muscle was initially stretched

by 20 grams. This is again in keeping with the observations made on gastrocnemius (see the last column in table 11). These observations indicate

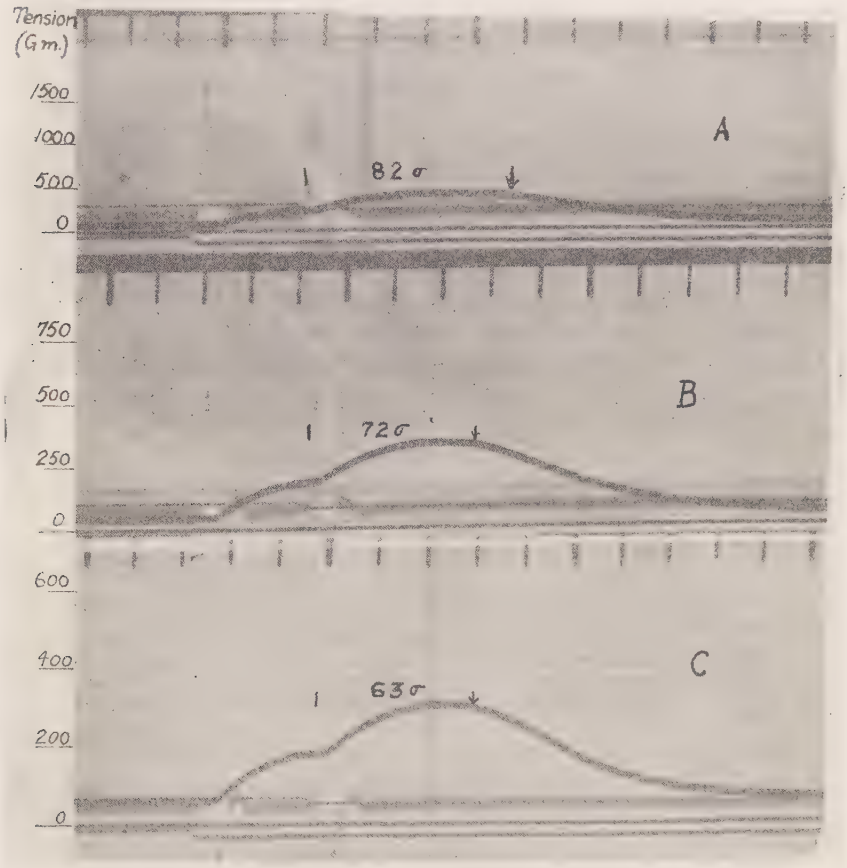

FIG. 81. Double responses of frog's gastrocnemius in which various degrees of shortening occurred. The first electrical response is approximately constant in the three responses while the second one is smallest in C in which the shortening was most extensive. The durations of the second response in A, B and C are respectively 82, 72 and 63σ. The stimuli were both break shocks given by magnetic signals whose shadows show on the plate above and below the galvanometer string. Time above = 0.02 second. String tension 8 mm. per millivolt (*361*).

that successive diminution in the electrical responses is at a minimum: (1) when tendon shortening is prevented; (2) when the initial stretch is great;

(3) and when in a parallel-fibred muscle where diminution is less marked than in a muscle with diagonally arranged fibres.

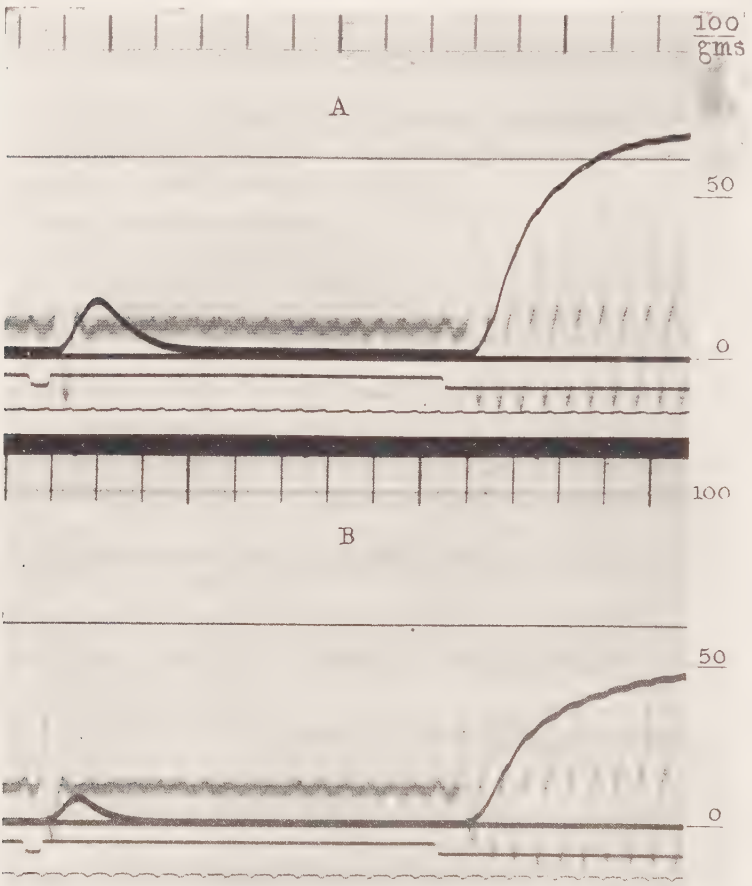

FIG. 82. Showing twitch and ascent of intact sartorius at 17° stimulated through its nerve (*353*).

A. Three grams initial tension: electrical responses during the ascent of almost uniform size. Electrical response of twitch, 15.5 mm.

B. One millimeter shortening permitted before becoming "taut." Electrical response of the twitch 10.5 mm. Note the increasing size of the electrical responses during the ascent.

This can leave but one conclusion, namely, that successive diminution in size of the electrical responses during the mechanical ascent of a tetanus is

associated with *shortening* of the individual fibres. The reverse of this, namely *lengthening* of the fibres during a response, should cause an increase in size of the electrical responses. This has been investigated incidentally

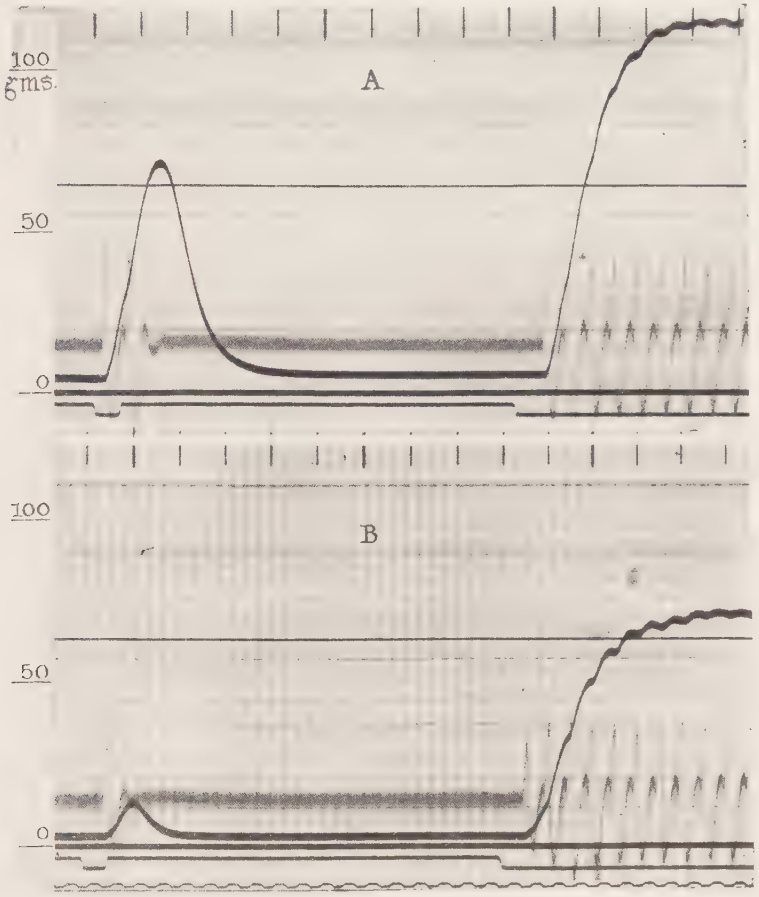

FIG. 83. Another sartorius preparation. Conditions as in figure 82 (*353*).

A. Initial tension, 6 grams; plateau tension, 115 grams; first response, double; note smaller size of second electrical response (also in tetanus).

B. Same. One millimeter shortening permitted (line of zero tension improperly set). String at exactly the same tension as in A (58 m. per ampere). Note the size of the first three, and the fourth action currents in the ascent.

in experiments recorded in an earlier chapter (VI). If one lumbar root, "B," is stimulated for a brief interval during the plateau caused by tetaniza-

tion of the other root, "A," the muscle, as a result of the new fibres brought into play by the second root, shortens further (fig. 71). During the terminal plateau response resulting from the stimulation of B, the action currents of root A are smaller than before stimulus B owing to the more shortened state of the fibres. But during the relaxation from the response of B, *i.e.*, when the fibres of A (and B) are lengthening, the electrical responses increase in size *pari passu* with the lengthening of the muscle (see page 188 and fig. 71).

It will be seen that these observations are in keeping with those of Samojloff (1908, *837*, *838*) in which he found that no diminution in size of a second action current occurred if the response were made rigidly isometric.

Isotonic responses. To distinguish the respective influences of tension and shortening, experiments have been made in which the gastrocnemius muscle, stimulated as in the previous responses, was allowed to shorten isotonically. Under such circumstances marked diminution occurs in the size of the successive electrical responses during the ascent, *i.e.*, during the period in which the muscle is *raising* the weight (fig. 84 C). During the plateau in a given tetanus (when the muscle merely *maintains* the weight) the electrical responses are, as in an isometric response, all of equal amplitude, but the galvanometric amplitude in millimeters of the action currents during the plateau in any response appears to be a complicated function of the weight maintained. The greater the weight (and hence the length) the larger the plateau electrical responses, but the greatest variation appears to occur between small increments of relatively low tension. Thus, when maintaining ± 3 grams (fig. 84 A) the successive deviations of the galvanometer were 9 mm. during the plateau, while with 50 grams (fig. 84 B) they were 15.0 mm., but with 250 grams they were only 16.5 mm.

A further point noted in the isotonic records is that the absolute length of the muscle during the plateau of its (tetanic) response does not undergo great variation for weights as high as 80 to 100 grams.[3] Thus to lift passively 100 grams a gastrocnemius muscle is lengthened approximately 3 mm. more than when lifting similarly 10 grams. During a tetanus the weight of 100 grams is raised approximately 3 mm. higher than a 10-gram weight is raised. The length of the muscle during the tetanus plateau is, therefore, very nearly the same in the two instances. This excludes the possibility that the variations in size of the "plateau" electrical responses with varying

[3] When these observations were first communicated it was not realized that variations in length as small as 0.1 mm. were capable of producing relatively large variations in the electrical responses. The results obtained with isotonic responses are not therefore out of harmony with those observed with the torsion-wire lever.

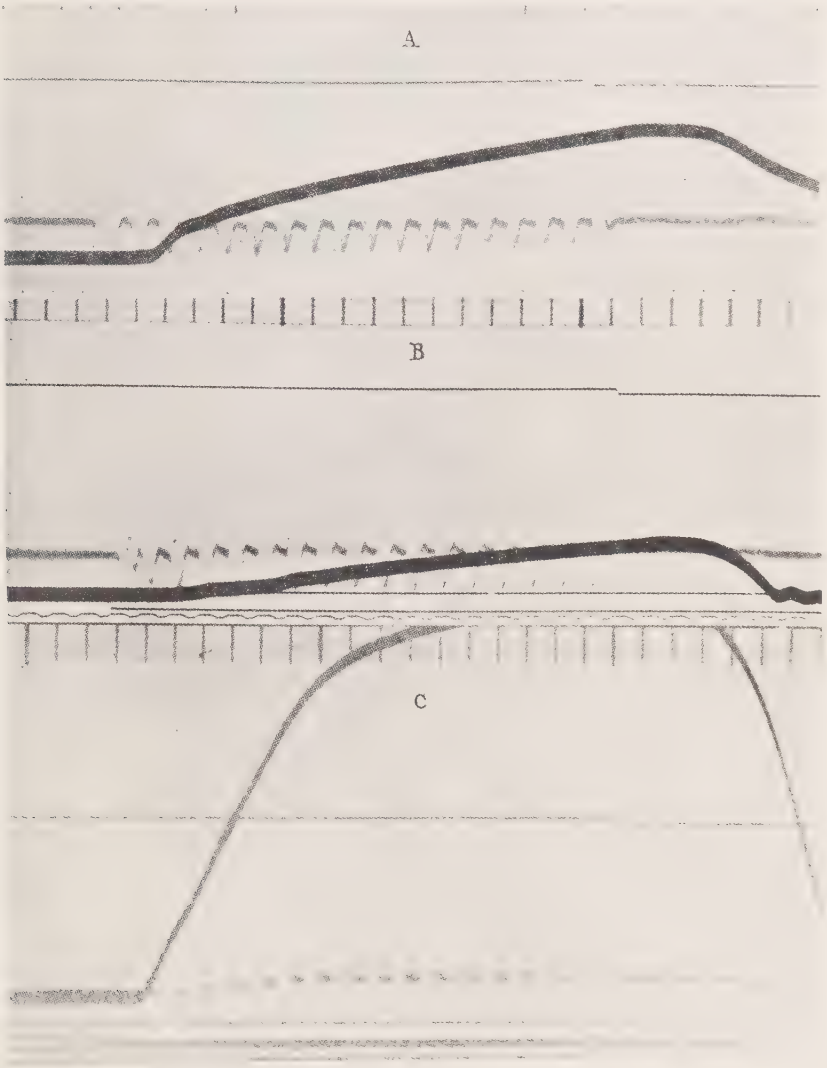

FIG. 84. Isotonic responses of an intact gastrocnemius at 17° stimulated as in the previous experiments. Time above 0.02 second (*353*).

A. Load, ±3 grams; first response, double. Note size of plateau responses.

B. Same muscle "after-loaded" with 50 grams; 4 mm. shortening allowed before lifting weight.

C. Same muscle initially loaded by 50 grams. Note diminution in successive responses during the ascent.

weights were produced mechanically by gross variation in distance between the leads. Slight differences of muscle length with increasing weight undoubtedly existed, which would be sufficient to account for the variations in the electrical responses during the "plateau."

AUGMENTATION IN SIZE OF SUCCESSIVE ACTION CURRENTS DURING THE MECHANICAL ASCENT

Diminution in the size of the successive action currents during the mechanical ascent is to be observed so long as the muscle is under at least 5 to 10 grams initial passive tension (*i.e.*, "taut") at the beginning of the response. One may now discuss the reverse condition in which an *augmentation* of the successive electrical response is observed.

Responses obtained with the torsion-wire lever. If the sartorius or the gastrocnemius muscle completely freed from the connective tissue attachments of their tendinous insertions, is allowed to shorten from 1 to 5 mm. before developing appreciable tension, a progressive augmentation in the size of the successive action-currents is observed during the mechanical ascent of the tetanic response. The mechanical condition of the muscle is under these circumstances such that 90 per cent more or less of the total shortening taking place during the response occurs *before appreciable tension is developed.* In one experiment records were taken in which 5.0, 4.0, 2.5, 1.0, and 0 mm. of shortening of the tendon were permitted before the muscle became "taut." These were followed by a sixth response at 45 grams initial tension. The first four and last records of this experiment are shown in fig. 85;[4] the last shows the characteristic diminution in the electrical responses during the ascent, while the first four show various degrees of augmentation. We have seen that the effect of tendon shortening on a "taut" muscle is to reduce the size of the electrical responses. This effect is also seen in these experiments, for as figure 85 A-D shows, after the maximum augmentation has been reached the electrical responses again diminish in size (table 13). Augmentation, therefore, occurs *in spite* of the normal tendency of the responses to diminish as shortening occurs. The entire

[4] In the first part of the research a string was used, one terminal of which "leaked" to the earthed mounting. Owing to the fact that the camera with the short-circuiting keys were to some extent earthed through floor, it was impossible on damp days to prevent a small periodic movement of the string when the separation keys were moving (see figs. 81 and 84). As it did not increase in size when the short-circuiting keys were open,—the electrodes touching another part of the preparation,—it does not interfere with the interpretation of the action currents. The terminals of the galvanometer were later completely insulated from the mounting and the difficulty was overcome.

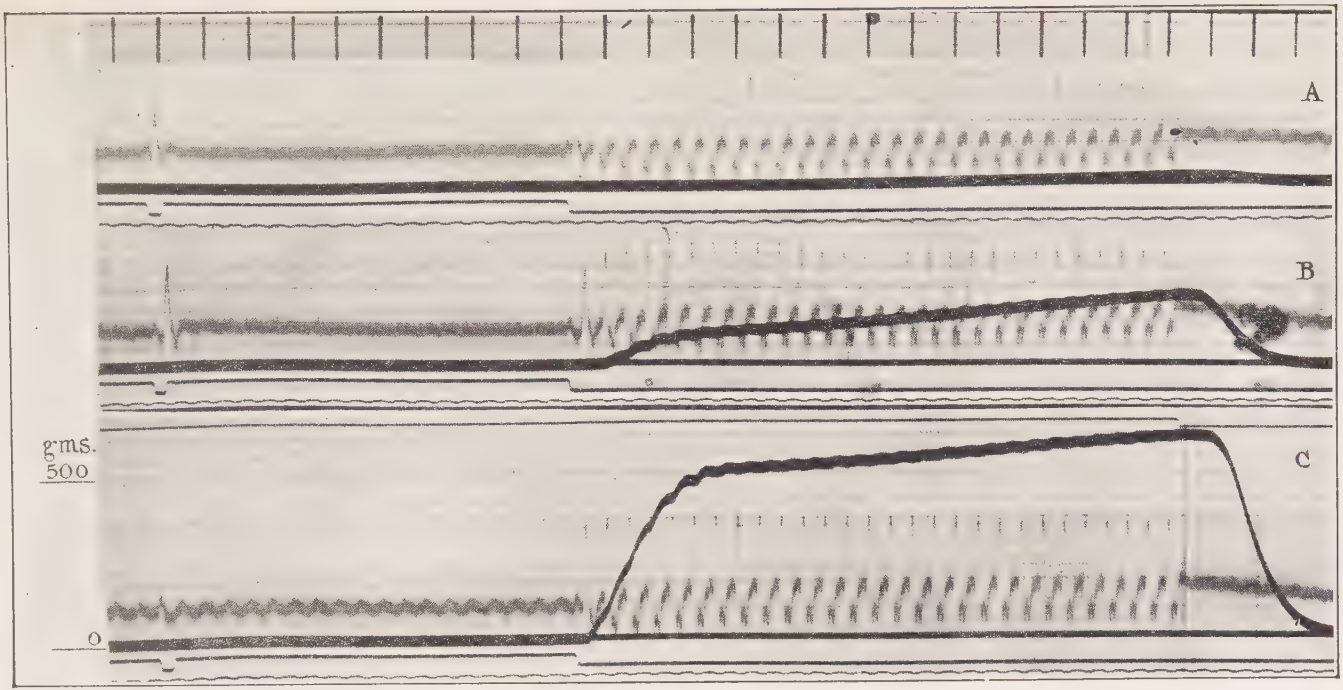

FIG. 85. Intact gastrocnemius at 24.5°. String at 50 mm. per ampere throughout; measurements of tension and electrical responses given in table 13.

A. Five millimeters shortening permitted before becoming "taut." Mechanical response scarcely visible.

B. Four millimeters shortening permitted; mechanical response of twitch as in A not visible.

C. Two and one-half millimeters shortening permitted. As short-circuiting key was not open sufficiently long in this record the impulse for the twitch did not "get through." Its size may, however, be inferred from the first response of the tetanus. Note the increasing size of the first electrical responses in the tetanus.

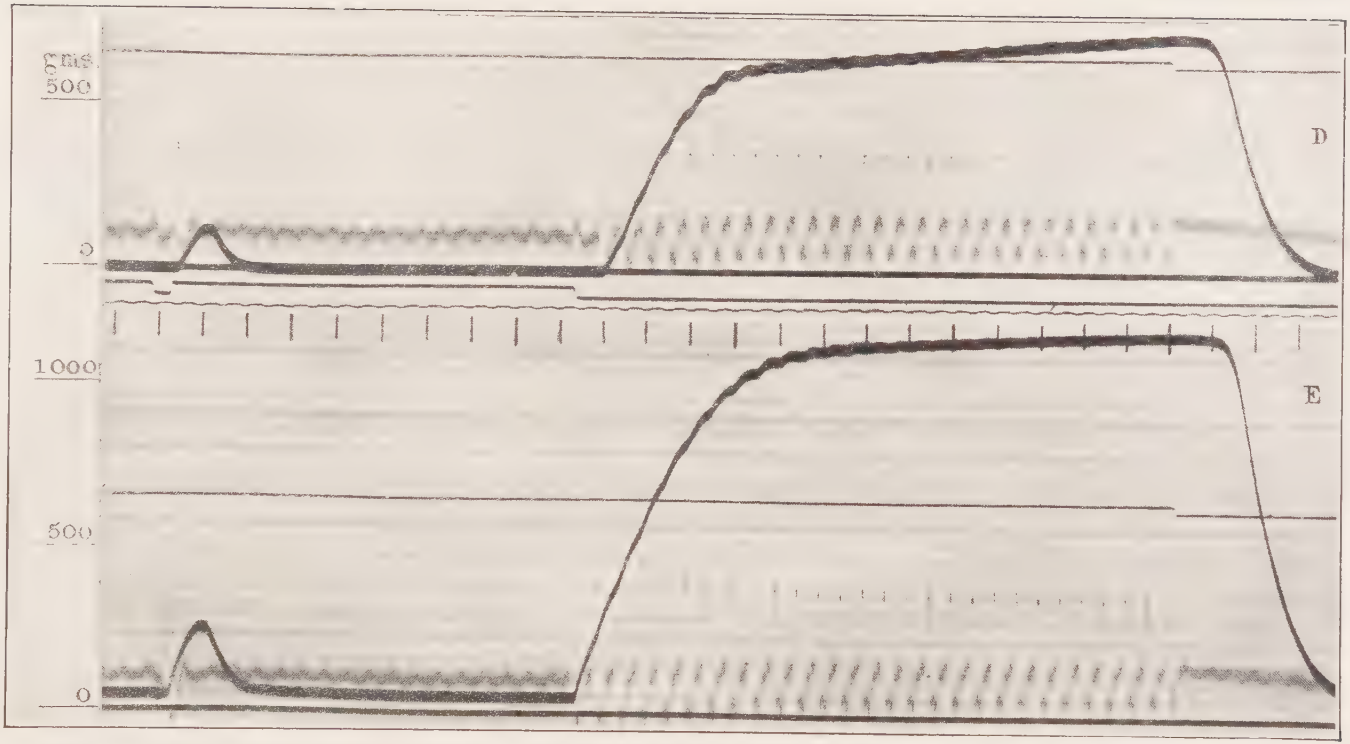

FIG. 85. D. One millimeter shortening permitted. Note the flat top in the mechanical record of the twitch, and that the electrical responses are nearly of equal size during the ascent.

E. Forty-five grams initial tension. Note diminution in electrical responses.

experiment is summarized in table 13. The results there tabulated have been confirmed in twenty similar experiments. Another record of a similar experiment is shown in figure 86. In this the alteration in size of the plateau electrical responses is particularly marked. The augmentation of the electrical responses during the ascent of sartorius was observed in seven experiments (figs. 82 B and 83 B). If a small amount of tension (1 to 2 grams) were applied either to sartorius or to gastrocnemius the responses became of almost equal size during the ascent (fig. 85 D), but if it were increased still more the progressive diminution during the ascent was then observed (fig. 85 E).

TABLE 13

Showing the increase in size of electrical responses during the ascent when shortening is permitted before the development of external tension

(Conditions in legend of figure 85)

SHORTENING PERMITTED BEFORE BECOMING "TAUT"	PLATEAU TENSION		SIZE OF ELECTRICAL RESPONSE (DIPHASIC EXCURSION)			
	Twitch	Tetanus	Twitch	Tetanus		
				First response	Highest response	Last response
5.0 mm.		10(?)	7.5	7.0	14.0	12.0
4.0 mm.		295	9.0	9.0	14.5	12.5
2.5 mm.	(95)*	600	(13.5)	13.5	16.0	13.5
1.0 mm.	118	710	16.0	15.5	16.5	13.5
0 mm.†	135	795	27.0	25.5	(First)	14.0
45 grams tension	215	1250	31.0	30.5	(First)	15.5

* Absent, but inferred from the first response of the tetanus.

† Tension, 1–3 grams.

Isotonic (after-loading) responses. The isotonic equivalent of the experiment tabulated in table 13 is an experiment involving after-loading. This was done (the preparation being arranged in the usual way) by finding the point at which the muscle just moved the weighted isotonic lever. The moist chamber containing the preparation was then raised in routine experiments 4 mm. In an ensuing response, therefore, the muscle shortened 4 mm. before lifting the weight. Under these conditions, whatever the weight might be, there occurred a progressive augmentation in the size of the first two to ten electrical responses (fig. 84 B). The amount of the augmentation increased with the weight lifted, and as in the case of the plateau responses described above, there was a much greater augmentation between 5 and 50 grams than between 50 and 250 grams.

For comparison records taken with the muscle after-loaded by a given weight were immediately followed by responses in which the muscle was stretched initially by the same weight (fig. 84 B and C) as described above. In both cases, whether after-loaded or initially stretched by the same weight—one producing augmentation, the other diminution of the responses in the ascent—the action currents during the plateau, when the weight was

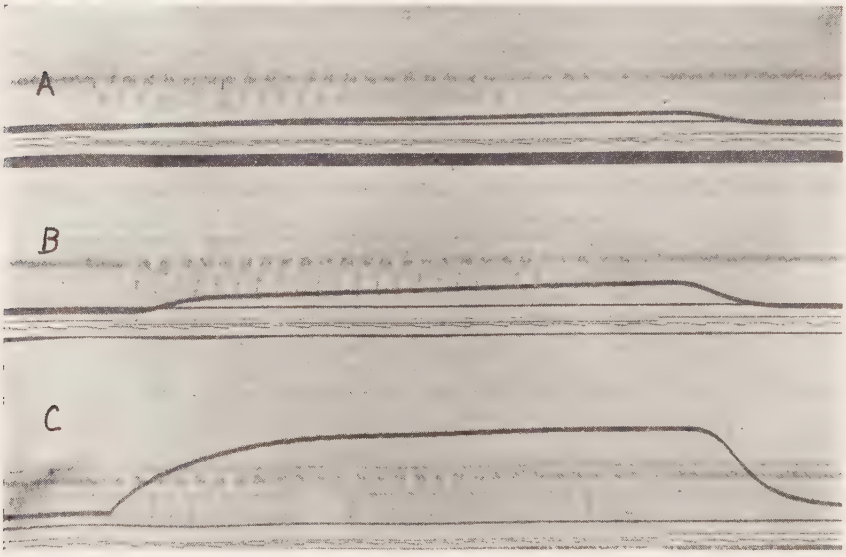

FIG. 86. Responses of an intact gastrocnemius under conditions similar to those in figure 85 but at lower temperature (13°). In this the increased size of the plateau electrical responses with increased tension development is very marked. In A in which only 60 grams was developed, the muscle being initially slack, the plateau electrical responses were 8 mm.; in B with 150 grams tension they were 10 mm.; and in C with 600 grams they were 13 mm. Note also the successive diminution in C; the first electrical response in this record is 17.5 mm. in amplitude, so that as between the smallest action current in A and the largest in C there is a diminution of about 55 per cent in amplitude. In a large number of similar experiments the corresponding maximum ratios has seldom been above 60 per cent. In this record A was taken first and C last so that any heating of the string occurring between the responses would have tended to have made the last the smallest. Rate of stimulation; 28 per second.

merely being maintained were of equal amplitude. In figure 84 B, in which the muscle was after-loaded by 50 grams, the first electrical deviation is 9 mm., while the plateau deviations are 15 mm. in amplitude; in figure 84 C, on the other hand, in which the same muscle immediately after the response

was initially loaded (stretched) by 50 grams the first action current is 25 mm. and the plateau responses 15 mm. in amplitude. The general result has been obtained in twelve experiments.

The reversal in the behaviour of the action currents during the ascent excludes the possibility of the variations having been produced mechanically by alteration in the distance between the leads. If, for example, the augmentation during the ascent in figure 84 B had been produced by a lowering of the resistance between the leads as they became closer together (making the resistance of the source more favourable with respect to the galvanometer string, so producing larger deflections), it would be impossible to account in this way for the reverse picture in figure 84 C on which the responses become successively smaller as the leads become more close together. It is evident, from these observations, that while alterations in the distance between the leads might modify slightly the size of the successive responses it is not a large modification and consequently does not destroy the value of the observations. This conclusion is strengthened also from the fact that the apparent size of the injury and demarcation currents has seldom been observed to alter in these experiments when passively increasing the length of the muscle. When once these currents have been balanced, they nearly always remain so (when the temperature is not altered) throughout a large range of initial tensions, irrespective of what form of lead (AgCl or $ZnSO_4-NaCl$) was used. This would not be the case if alterations in the distance between the leads produced a large percentage alteration in the total resistance.

No adequate explanation has yet been found for the progressively increasing magnitude of successive action currents when a muscle commences tetanic activity in a slackened state. It was pointed out originally (*353*) that the phenomenon gave evidence of a condition in which the size of action currents varied independently of muscle length, and it was suggested that possibly under these circumstances tension *per se*, rather than length governed the size of the electrical variations. The fact remains, however, that when a small degree of initial tension is present the size of action currents in an ensuing contraction does vary with length of the fibres. It has been found, moreover, that whether the muscle commences activity initially "taut" or initially slack, the size of successive action currents during the mechanical plateau varies directly with the length of the fibres during the plateau rather than with the tension developed.

It is possible that the augmentation of the action currents when initially slack is due to something akin to the "treppe" observed by Waller (*1017*) in the case of *nerve* action currents, and attributed by him to the liberation of carbon dioxide within the nerve. This may be the case, but one must remember that no such phenomenon has ever been observed when a muscle commences activity initially "taut." The effect would, therefore, appear to be associated with the tensile relations of the individual fibre.

The reasons for believing that the effect is not due to purely physical causes (rather than to physiological) have already been considered above.

SUMMARY

Conditions influencing the size of the recorded electrical responses of contractile tissues have been considered in detail, and the only factor which will account for the observed alterations during tetanic responses is that the size of the action current of individual fibres varies with varying mechanical conditions of activity. If a fibre is permitted to shorten during a tetanic response of 50 per second, the successive electrical responses become progressively smaller until the muscle ceases to shorten, at which time the electrical responses become of constant size. If shortening during activity is altogether prevented, no alteration occurs in the size of successive action currents. A corollary to these two observations, namely, the *more* a muscle shortens during activity the *greater* the progressive diminution in size of successive action currents, has also been found to hold experimentally. But these generalizations are only true provided the muscle as a whole at the beginning of contraction is under appreciable initial stretch (1 to 3 grams).

When the muscle is initially so slack that it must respond several times before developing appreciable tension on the recording lever, the successive electrical responses progressively *increase* in size. No satisfactory explanation of this observation has been found, though there are adequate grounds for believing that this augmentation of the action currents is due to genuine alterations in size of the constituent electrofibregrams. The possibility that it is a phenomenon akin to the "treppe" observed in the electrical responses of nerve by Waller (*1017*) has been considered. The size of the "plateau" of electrical responses, whether the muscle starts initially slack of initially "taut," varies directly with the length of the muscle during the plateau and *not* with the tension developed. This is true both of responses obtained with isotonic levers and with an "isometric" torsion-wire lever. The probable significance of these observations will be considered in the next chapter.

CHAPTER VIII

The Significance of the Action Current of Skeletal Muscle

Since the discovery of animal electricity by Galvani (*376*) in 1794[1] the nature and significance of the phenomenon has been deeply studied and many significant facts have been brought to light. The early investigations upon the "negative variation" (du Bois-Reymond) turned largely upon the relation of the electrical response to muscle irritability. The time relations of the electrical and mechanical responses, though considered by the early investigators, were not accurately worked out until the question was taken up by Burdon Sanderson (*179*). It came to be generally recognized as a result of his investigations that the electrical response occurs during the latent period of the mechanical response, but the existence of an intimate functional relation between the two was considered unlikely, and many early investigators looked upon the negative variation as a chance concomitant of contractile activity.

As a result of the all-or-none principle, the prevailing belief concerning the action current of a muscle fibre appears to be (as with the negative variation of the nerve fibre) that it is of constant size (Lillie, *645*, p. 334) under all circumstances, save during the relative refractory period. In the words of Forbes and Cattell (*319*, p. 166): "the size of the propagated disturbance is independent of the strength of stimulus, provided this is adequate," and the disturbance "appears to be essentially the same in nerve and muscle. In each case its progress along the fibres is marked by the electrical response or action current." Several attempts have been made in the past to correlate the electrical response with functional activity of the fibre, but the general impression one gains from reading the work of previous investigators in this field is that expressed by Forbes, Ray and Hopkins (*331*, p. 301): "the action current in response to a single stimulus, may have little or nothing to do with the tension activity developed by the contraction of the muscle, for it is well known that this action current has passed its maximum before the mechanical response has appreciably altered the tension." This view as to the independence of the electrical response and contractile activity, early maintained by Bernstein (*88*, 1871), and tacitly assumed by many later authors (Biedermann, Engelmann, Härtl), is to some extent contradicted by facts already known.[2]

Lamansky (*575*, 1870), Rivière (*815*, 1898), Schenck (*851*, 1896), Bernstein (*91*, 1897), Samojloff (*837*, 1907), and Forbes, Ray and Hopkins (*331*, 1923) all found that the size

[1] The circumstances of Galvani's discovery are described in the Introduction.

[2] A useful account of the investigations in this field before 1900 is to be found in Mendelssohn's (*706*, p. 331) paper in Richet's *Dictionnaire*.

of the action current in the twitch of the gastrocnemius of the frog is increased by increasing the initial tension of the muscle. Burdon Sanderson (*180*, 1895), Buchanan (*174*, 1901, p. 134), and Forbes, Ray and Hopkins (*331*, 1923) failed to find any alteration of the action current with tension in the parallel-fibred sartorius, and the last authors concluded that the increased electrical response in gastrocnemius is an artefact caused by the diagonal disposition of the fibres. According to their view, when the muscle is extended the fibres become more nearly parallel, with the result that there is less tendency for the action currents in adjacent fibres to interfere with one another. Against this view is the fact that Bernstein (*91*, 1897), and Bernstein and Tschermak (*93*, 1902), who used the adductors of the frog which are also parallel-fibred, and Schenck (*851*, 1896) who used sartorius, found that tension distinctly altered the size of the action current. Bernstein and Tschermak also noted that if the tension was very greatly increased the size of the electrical variation passed through a maximum. Schenck performed the interesting experiment of tetanizing a muscle at a low frequency and alternatively increased and lowered the tension of the muscle during the response. He found both in gastrocnemius and sartorius that the electrical responses increased and fell with the mechanical tension. Samojloff (*838*, 1908), using the capillary electrometer, made the important observation that if during an isotonic twitch a second stimulus be delivered after the relative refractory phase, the second action current is smaller than the first, and is smallest at the time of maximum shortening. If the contraction were made rigidly isometric the diminution in the second response did not occur, and it was inferred that the development of tension in an isometric contraction tends to prevent diminution in the size of the action current.

But few investigators as far as I have been able to discover have suggested that a relation exists between the size of the electrical response in muscle and the work done in contraction. These were Rivière (*815*, 1898) and Athanasiu (*38*, 1912). The former noted in isotonic responses that the heavier the weight lifted the larger the action current (gastrocnemius), but the precise conditions of loading, etc., are not clear from this author's description. Athanasiu noted that when the intact frog's gastrocnemius was in what he called a "régime permanent," *i.e.*, stimulated at 300 to 400 per second (too rapidly for the muscle to follow electrically) the main peaks in the action currents increased in size with the load, and he inferred that a relation existed between the electrical variation and work. A similar suggestion was also made on other grounds by Bernstein and Tschermak (*94*, 1904).

In considering the functional significance of the electrical response it is of first importance to establish its time relations with accuracy. This has been considered in Chapter II. It is permissible to repeat here that the interval between the commencement of the electrical response and the mechanical activity is notably brief, but there apparently is always a small interval, *i.e.*, mechanical activity of the muscle never precedes the electrical activity. This in itself suggests that the electrical response represents, or is an index of the process which causes the muscle to enter into activity. Observations on direct stimulation of nerve show us that the electrical response is practically simultaneous with the stimulus; at least the interval not greater than 0.06σ (*287*), which is beyond the limits of experimental

error of ordinary recording methods. This means that the only interval between an adequate stimulus and the appearance of the mechanical response is that which normally occurs between the electrical response and the mechanical response. This interval has been termed the "true" latency. In mammalian muscle the interval observed is as small as 0.6σ ($1\sigma = 0.001$ second); the interval for amphibian muscle is 1.5σ. As the same instrument was employed in the two cases it is evident that the interval is genuine, at least it is not the result of instrumental delay. In view of this one may well ask whether under any circumstance it is possible to have an electrical response without a mechanical response. Are the two manifestations of activity separable?

THE POSSIBILITY OF SEPARATION OF ELECTRICAL AND MECHANICAL RESPONSES IN SKELETAL MUSCLE

Mines (*716*), as is well known, insisted that in the case of heart muscle the electrical response persists after the mechanical response had been obliterated through subtraction of certain electrolytes, notably calcium. He found, for instance, that when the heart of a frog had ceased to beat following perfusion with calcium-free salt solution, there remained small but nevertheless distinct rhythmic electrical responses. The same conclusion was reached by Noyons (*738*) using drugs, and more recently by Wiggers (*1047*). Mines's experiment has been repeated by a number of Dutch investigators (Einthoven and Hugenholtz, *271;* and Willigen, *1049*). The former authors found that if a mechanical recording device of a high degree of sensitivity were employed, and the heart gradually poisoned with KCl solution, the mechanical and the electrical responses diminish progressively to extinction. They also point out the great difference in the energy required to move the heart muscle as contrasted with that necessary to move a galvanometer string. They observed that the "sommets des mécanogrammes et de l'électrogramme deviennent simultanément et régalièrement plus petits," and concluded that the two phenomena are linked indissolubly (*271*). The result of Mines and others these authors attribute to inadequate mechanical recording methods.

It may be recalled that Biedermann (*103*), Englemann (*283–285*), and other early investigators believed that excitability, conductivity and contractility were independent and separable properties of irritable tissues. They found, for instance, that a hypotonic solution or distilled water often caused a disappearance of contractility without disappearance in conductivity. Thus, if one end of the sartorius muscle were water-logged and incapable of contracting it would nevertheless transmit excitatory disturbance to the undamaged end of the muscle (Härtl, *429*). Evidence of a similar nature was adduced when muscles were subjected to mild degrees of alcohol narcosis. De Boer (*114*) investi-

gated the problem in 1917 and found that in case of water rigor the œdema caused by the absorption of water, though it made further shortening impossible, did not prevent an internal movement of the sarcostyles, *i.e.*, shortening could not show itself, on account of the œdematous shortening already present in such muscles; thus, mechanical records could not be obtained though electrical responses were present. He suggested in view of this that the evidence of Härtl, Engelmann and others as to the independence of contractility and excitability was inadequate. Arbeiter (*34*) carefully reviewed the early literature of the subject and concluded on the basis of his own experiments that the properties of conductivity and excitability are inseparable. He perfused hearts with Ca-free Ringer and made the important observation that whereas the mechanical responses diminish rapidly during the first five minutes of perfusion, it sometimes required as long as twenty-four hours of perfusion of this solution for the mechanical responses to become completely non-existent. For his mechanical record he used the same instrument ("inscripteur à corde") as that employed by Einthoven and Hugenholtz.

Seliškar (*855*), on the other hand, reports that in his experience absence of calcium causes failure of the mechanical response of tortoise auricle *without* diminishing the rate of conduction of the electrical disturbance. He did not, however, measure the size of the electrical response, nor did he attempt to harmonize his observations with those of Arbeiter (*34*) and others (*30, 32, 270, 271*), who obtained contrary results. Moreover, if the *summits* of the action currents in Seliškar's figure (7) be used for determining the conduction rate, rather than the less accurate S-shaped beginnings of the deflections, a marked diminution in rate (following absence of calcium for 5 minutes) is evident.

Recent evidence, therefore, is against Mines's original interpretation and appears more and more to point toward the conclusion that the electrical and mechanical responses are in fact inseparable. Lewis (*629, 630*) has discussed the evidence *pro* and *con* and has decided in favour of de Boer and Einthoven, pointing out the inadequacy of Engelmann's contention regarding the independence of excitability, conductivity, and contractility of heart muscle. The conclusion is also supported by the recent experiments of Gasser and Hartree (*389*) who found that when poisoned with alcohol or hypotonic saline, heat and tension of the excised sartorius diminish *pari passu* and become extinguished simultaneously, *i.e.*, the curve correlating heat with tension passes through the origin. They remark also that "the present trend of the evidence is in the direction of showing that poisons destroy in muscle the process which is responsible for the manifestations, heat, tension, conduction, and potential change. It is safe to conclude that heat and tension never have been dissociated, and it seems likely that they cannot be."

Beritoff (*76, 79*) has recently raised the question as to whether electrical and mechanical responses of skeletal muscle are separable by means of fatigue. He found in certain instances that well-marked electrical responses remained when the mechanical tension had apparently subsided to a negligible amount.

The question was re-examined in the course of the present investigation and it was found that with a recording lever of enhanced accuracy, so long as an electrical response persisted during continuous stimulation, there also persisted a corresponding increment of mechanical tension. The gastrocnemius muscles of decerebrate frogs were stimulated (intact) over pro-

longed periods. The responses were photographed at the beginning of the tetanic stimulation, a sample was recorded in the course of the stimulation, and finally the end of the tetanus was recorded when the myograph lever owing to fatigue had almost returned to the base line. Such a record is

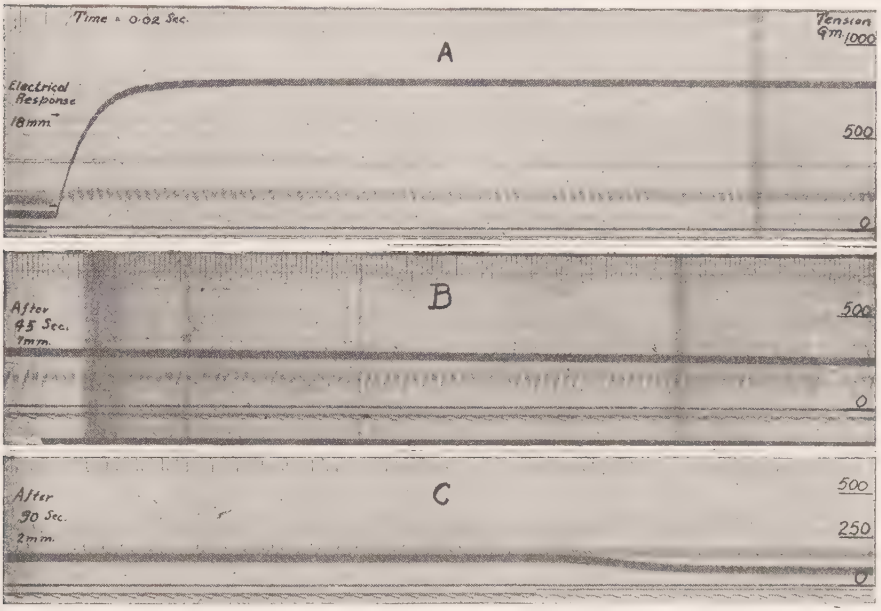

FIG. 87. Fatigue curves of the intact gastrocnemius (14°) stimulated indirectly. The stimulation is commenced in record A, continued in B after an interval of 45 seconds' continuous stimulation, and C is the terminal record of the same tetanus after a further interval of 90 seconds' continuous stimulation. It will be seen that the mechanical and the electrical responses diminish *pari passu*. The very small electrical responses in the last record are represented by a small residual mechanical tension which disappears after cessation of the stimuli. That the diminution in this response was not due to local excitation fatigue was tested in the response (between records B and C) by moving the electrodes up and down on the nerve and this caused no increase in the size of the response.

Note the size of the action currents in A as compared with B and C. Time above = 0.02 second. String tension 7 mm. per millivolt. A signal shows the commencement and cessation of stimulation in A and C (*362*).

shown in figure 87. It will be observed that during the middle exposure, which was taken 45 seconds after the end of the first exposure, the electrical and mechanical responses diminished progressively and proportionally. The lower exposure of this figure was taken 90 seconds after the end of the middle one (stop-watch). It will be seen that in this terminal

record the electrical and mechanical responses were very greatly diminished and the tetanus was terminated in the course of the record to show that the small increment of mechanical tension existed to account for the correspondingly small electrical variations. Twenty similar experiments yielded the same result and never in my experience has an electrical response existed without a corresponding mechanical response. And this is true whether the muscle is stimulated through its nerve or directly. The evidence in the latter case is less satisfactory owing to the difficulty in preventing the escape of stimulating currents. This was to some extent obviated by stimulating with alternate make and break shocks so that the action current would always be in one direction while the escape would oscillate.

The result is the same whether the muscle responds isometrically or isotonically, but in the latter case fatigue proceeds less rapidly owing presumably to the shorter length of the fibres. When maintained in a lengthened condition the energy liberation, stimulus for stimulus, is greater than when the muscle is allowed to shorten, and this undoubtedly accounts for the quicker fatiguability of the isometric response.

A point of interest in these experiments was that a distinct hyperpnoea was observed in a large number of the preparations following the fatigue stimulation. As the integrity of the circulation in a muscle was difficult to ensure, this observation was satisfying as giving indirect evidence that the circulation was active, and thus served as a useful control.

Andrus and Carter (*32*) and Drury and Andrus (*248*) have emphasized the importance of pH in controlling the rate of development of the excitatory process in cardiac muscle, and their results suggest that polarization of a muscle fibre is conditioned by a difference in hydrogen-ion concentration between the cell contents and tissue fluids. Andrus has pointed out that when a strip of mammalian auricle is placed in a solution of high pH (*i.e.*, alkaline) the rate of conduction increases, the size of the action current is augmented, and the size of the mechanical response is increased. When, however, the strip of auricle is perfused with a more acid solution the rate of rise of the action current diminishes and the rate of conduction diminishes correspondingly. When the pH is in the region of the iso-electrical point the electrical response disappears altogether. This suggests that the diminution of the action current which has been observed in case of fatigue is due to the diffusion into the tissue fluids surrounding individual fibres of acid metabolites, and that when the accumulation becomes sufficiently intense the polarization of the membrane is then destroyed. This is in keeping with Hartree and Hill's (*111*) observation that the greater the acidity of the

perfusate the slower is the rate of oxidative recovery in muscle. They found incidentally that the CO_2 ion was the most effective vehicle for carrying the hydrogen ion into the muscle cells, a result which harmonizes with the important observations of Jacobs (*517*, *518*) on membrane permeability.

THE RELATION OF THE SIZE OF THE ELECTRICAL RESPONSE TO THE LENGTH OF THE MUSCLE FIBRE (*361*)

We may now consider other relationships existing between the electrical and the mechanical responses. We have seen that the greater the tension developed by a given muscle in response to maximal tetanic stimulation the larger are the successive action currents, and that the mechanical conditions obtaining before and during stimulation determine the size of the mechanical response. However, under certain circumstances the length of a fibre varies independently of its tension development. It becomes an interesting problem, therefore, to determine whether the size of the action current varies with the length of the fibre or with its mechanical tension.

Under all conditions in which alteration in the length of the fibre occurs corresponding alterations in the size of the action current take place. These three conditions may be summarized briefly as follows: (1) In a twitch the size of the electrical response is greater the greater the initial length of the muscle. This has been found to hold true both for the sartorius, semitendinosus and gastrocnemius of the frog and for the rectus femoris and gastrocnemius of the cat. (2) In tetanic responses the same relation holds, the greater the initial physiological length of the muscle fibre the greater is the electrical response and the greater the tension developed. (3) When shortening occurs during a tetanic response the electrical responses are the largest when the shortening permitted is the least. This phenomenon has been described in detail in the previous chapter. It will be recalled that successive diminution in size of the electrical response occurs during the mechanical ascent and ceases during the plateau, when shortening ceases.

The size of the action current and the duration of the mechanical response. Under the circumstances just mentioned it was also found that the *duration* of the mechanical response varied with the size of the electrical response. Not only was the tension developed greater the greater the muscle length, but the duration of the mechanical response was always longer under any circumstance in which the muscle length was enhanced. In addition, therefore, to the size of the response there is an important correlation

between the *duration* of the response and the size of the action current. Six conditions in which the duration of the mechanical response and the size of the electrical response run a parallel course may be described. (1) In the twitch the greater the initial length the greater the duration of the mechanical response and the larger the electrical response. (2) Similarly in short tetani the greater the initial tension the more enhanced becomes the duration of the terminal mechanical response (Chapter V). (3) When the duration of a twitch is compared with the duration of the terminal mechanical response of a brief tetanus it is found that the latter is always briefer. The electrical response responsible for the latter is also always smaller, and the ratio

$$\frac{\text{Duration of twitch}}{\text{Duration of terminal tetanic response}} = \frac{\text{Twitch action current}}{\text{Tetanus "plateau" action current}}$$

is always approximately constant. In other words, when extensive shortening occurs during the tetanus, and the electrical response is in consequence very much diminished, the duration of the terminal mechanical response is correspondingly diminished. This is perhaps the most convincing evidence that the size of the electrical and the duration of the mechanical responses are dependent variables. (4) A corollary of the last consideraion is the fact well illustrated in figures 81 and 82 that the smaller the degree of freedom for shortening during the mechanical response the greater the duration of the terminal mechanical response of the tetanus. Thus, in the experiment cited in the last chapter (table 12), when but 0.05 mm. shortening is permitted by connecting the muscle with the myograph at a point very near its axis, the tension developed was 710 grams and the ratio between the size of the "plateau" electrical responses and the first electrical response is 0.71, while with 1.03 mm. shortening the tension developed is 543 grams and the ratio between the first and the last action current 0.54. In the first case the duration of the terminal response was 140σ while in the last its duration was only 90σ. In keeping with this observation it has been found that successive diminution in size of the electrical responses during the tetanus can, as we have seen in the last chapter, be prevented altogether if no shortening is permitted during the response. Owing to anatomical arrangement of the gastrocnemius it is impossible to prevent shortening of individual elements, but in sartorius the conditions can be realized in which no alteration in length occurs during a response, and in this muscle it is possible to prevent successive diminution of the electrical responses. (5) It has been found that submaximal responses are of greater duration than maximal responses. In the submaximal response the individual

elements shorten less than when assisted by surrounding fibre units as in a maximal response. It is therefore in keeping with the previous conditions under which alteration in the duration of the mechanical response has been observed. (6) A somewhat special case in which alterations in the duration of the mechanical responses have been observed was that described in Chapter IV in which it was found that when a response occurs during the mechanical ascent or during the plateau of a previous response, the duration of the second response is augmented by the incompleted processes of response I. It was accordingly suggested that this augmentation in duration is due to the as yet unexhausted acid ions liberated by the first stimulus.

As already intimated, these six conditions have one common feature, namely, that the greater the length of a fibre the larger the action current and the greater the duration of the mechanical response. This suggests that the electrical response is intimately associated with the underlying physico-chemical process which determines the extent of the energy liberation in muscle. The more the energy liberated the longer the time required for the ions so released to dissipate themselves, at least this seems a fair inference from the greater duration of the mechanical response. Hill and Meyerhof (*477*, *709*) have shown that as the length of the muscle fibre is increased within certain limits the energy liberated, as measured thermally, is also increased, and there is also direct mechanical evidence of an increase of the energy liberated by a muscle as it is initially elongated (Chapter VI). It would appear, therefore, to be somewhat more than a coincidence that the electrical response thus follows roughly the alterations in the energy liberation of a muscle fibre as measured by its heat production, and we may put ourselves the question whether the electrical response is not an index of the process by which energy is released, rather than a chance concomitant of activity.

THE RELATION OF THE ELECTRICAL RESPONSE TO HEAT PRODUCTION

The recent publication of A. V. Hill's useful book on muscular activity (*479*) makes it unnecessary to deal here extensively with the investigations on heat production. It is sufficient to outline the recent developments in order to show their relation to electrical phenomena.

We owe to the genius of A. V. Hill and his collaborators the separation of thermal responses of muscle into discrete phases correlated with mechanical activity. In 1913 Hill separated the thermal response of muscle into an initial phase and the phase of recovery and noted that the two were of approximately equal magnitude (*472*). von Weizsäcker (*1039*) observed that the initial phases of heat liberation occurred in the absence

of oxygen, while Hill and Hartree (*482*, *441*) subsequently demonstrated on the other hand that the greater portion of recovery heat *is* dependent upon the presence of oxygen. Hill and Hartree divided the initial heat production into three phases (*482*): (1) an initial outburst associated with mechanical shortening or possibly in part preceding mechanical shortening; (2) a steady production associated with the maintenance of tension; and (3) a second outburst associated with mechanical relaxation of the muscle. When under approximately isometric conditions this final outburst is due in large measure to the potential energy stored in the lever, which delivers a rapid stretch to the muscle during relaxation (see also *437*, *438*).

Hill, Doi, and others have pointed out that initial heat production varies with the length of the muscle, passing through a maximum as the initial length is increased beyond normal physiological limits. Hill has recently made this problem the subject of a more detailed investigation (*477*). He permitted a sartorius muscle of a frog to contract (isotonically) from a length "100" to "95," "90," etc., down to "50," and then to record an isometric contraction at the new length. It was found that (with length "100" as that at which maximum heat production occurs) heat and tension diminished together on a curve which is directed toward the origin. When the muscle had shortened to about 50 per cent of its "maximum length" it ceased to develop tension, but a small residual thermal response remained.

It will be seen that these observations form a close parallel to the behaviour of the electrical response under corresponding circumstances. When a muscle shortens its electrical response becomes progressively smaller as the shortening proceeds, and becomes of constant size when the shortening ceases,—the more the shortening the greater the electrical diminution. Quantitatively the diminution in the electrical response also bears a close relation to the diminution from heat liberation. In the case of the latter there occurred a diminution of approximately 50 per cent as between a length of "100" and a length of "50." Under corresponding circumstances the size of the electrical response diminishes approximately 50 per cent. The first electrical response in an isotonic tetanus in which the muscle shortens to its maximum amount is about double the size of the electrical response occurring during the mechanical "plateau." For other parallels between heat and the electrical response see *361*.

These observations suggest that the electrical response is produced by the same mechanism that controls the initial energy liberation in muscle. This being the case, we are reminded of the membrane which Hartree and Hill have postulated as necessary to account for the alteration of energy liberation in muscle with increasing length. It would seem that this can be no other than that responsible for the electrical response. When the muscle length is increased changes occur at this interface which lead on the

one hand to a larger electrical response and on the other to a greater liberation of energy. Since electrical variations result from the passage of ions it would not appear futile to suggest that the ions which produce the electrical response are identical with those which lead to the liberation of lactic acid.

THE MECHANISM OF THE RELEASE OF ENERGY IN MUSCLE

Little is known concerning the mechanism of energy liberation in muscle. The investigations of Hill and others have disclosed what takes place during the later stages of contraction, but as to what occurs in the early stages and how it is brought about we are almost entirely ignorant. The membrane theory of excitation and conduction has led to the belief that the electrical response of an irritable tissue is caused by a wave of permeability (see especially McClendon, *700*, *701*), and Hartree and Hill have suggested that the wave of permeability in the case of muscle causes the ionic disturbance which leads to lactic acid liberation. The intimate association which we have observed to exist between the electrical and mechanical responses clearly favours this hypothesis. It is permissible, therefore, to consider the possible nature of the ionic interchange associated with the wave of permeability.

The nature of the ionic changes responsible for energy liberation. The recent investigations of Embden (*273–278*), Milroy (*61*), and their coworkers make it evident that during activity there occurs a redistribution of ions within the fibres of a muscle. We have only to assume that this shifting of ions results in an alteration in the glycogen-hexosephosphate-lactic acid equilibrium in favour of the formation of free lactic acid, but let us not overlook the fact that this is as yet a pure hypothesis. In considering the specific nature of the ionic complex which causes a shifting of the equilibrium of our carbohydrate system, the following observations are of importance.

Embden in a long series of investigations which were commenced in 1913, has accumulated an important body of evidence, by some regarded as conclusive (but cf. Hill, *479*, p. 59), that the H-ions responsible for contraction are produced from a hexosephosphate body (the "precursor") as lactic and phosphoric acids. Embden and Lange (*276*) believe that following a stimulus changes in permeability of the postulated "sarcoplasmic" membrane which cause splitting off first of phosphoric and then of lactic acid from the precursor. On account of the higher degree of dissociation of lactic acid and the fact that previous thermodynamic calculation on the basis of lactic acid alone have given remarkably concordant results (*479*,

484) the view that phosphoric acid is a causal agent in bringing about contraction is not generally accepted.

The reaction, hexosediphosphate $\rightleftarrows$ phosphoric + lactic acid, appears to be reversible, and equilibrium, though clearly dependent upon the law of mass action (Milroy, *61;* Embden, *274*) is largely influenced and controlled by other ions which do not appear to take part directly in the fundamental reaction. Embden and Lange (*277*) have found that when a muscle is placed in isotonic cane sugar solution (which rapidly leads, as is well known, to inexcitability) there occurs a sharp rise in the O_2 consumption followed by a large diffusion of phosphate out of the muscle into the solution and, if chloride is in the solution (Embden and Lange, *277*), a large "Eintritt" of chloride ions into the muscle. When paralyzed in this way the power of various cations to restore the excitability of muscle follows the Hofmeister series. Sodium fluoride and nitrate were found, for instance, to produce a well-marked synthesis of the hexosephosphate "precursor" (Embden and Lenhartz, *278;* also Beattie and Milroy, *61*) from phosphate and carbohydrate (or lactic acid). When a muscle, paralyzed by cane sugar, is placed in Ringer solution excitability quickly returns and this is associated with a sharp fall in the rate of respiration together with an absorption of phosphate if it be added to the solution.

When a muscle is stimulated electrically, similar ionic changes occur—namely, an in-flow of chlorine ions during the increased permeability and which is compensated for by an outflow of phosphate and lactate. And if fatigued to inexcitability the same changes were observed to occur during the period of recovery as in the case of muscle "fatigued" by cane sugar.

The investigations of Embden, Meyerhof, Beattie and Milroy and others on the ionic interchange and metabolism of muscle are important contributions to our knowledge of muscular processes. Yet the methods which the present state of chemical knowledge renders it necessary to employ in these experiments makes one hesitate to regard their evidence as conclusive. "Chemists must invent far finer and more rapidly reacting tools before they can hope to get inside the mechanism, and to examine anything but the initial and final products of activity" (*479*, p. 65). It will be recalled that in most cases the technique demands freezing of the muscle (*e.g.*, with liquid air) followed by mincing of the tissue for lactic and phosphoric acid determinations. The fluoride syntheses were also carried out in minced muscle. While there is some reason for believing that the syntheses which occur in the intact fibres of a muscle may resemble those occurring in a minced tissue, it is quite improbable that the details of concentration, conditions of equilibrium, etc., can be inferred from experiments of this kind. The permeability of physiological tissues, and hence their conditions of equilibrium, are often upset by the most trivial circumstance. We have seen that when a muscle is transferred from the body into Ringer solution it no longer gives normal responses. One may also recall the point which Irving and Kay have recently demonstrated (*514*), namely, that when blood is

withdrawn into any artificial container, clotting being prevented by heparin, or any other anticoagulant, sugar is invariably found in the corpuscles; but when a quantity of blood is removed within a blood vessel, as by ligating a stretch of jugular vein, the corpuscles, after centrifuging the blood contained within the vein, are without sugar.

Calcium in certain concentrations (Lange, *578*) and in the presence of certain other ions causes the break-down of the precursor; under other circumstances it leads to its synthesis. This is of importance since it is clear from other and quite different evidence that equilibrium of a resting muscle depends among many factors upon the existence of a proper ratio of Ca and K ions. It is well known that these two ions are antagonistic (Bayliss, *59*). Excess of Ca, whether caused by an actual excess or by an absence of K, leads to rigor; in the case of the heart, stopping in systole. Excess of K whether caused by increased concentration or absence of Ca (as in Arbeiter's experiments referred to above), leads to inexcitability, inhibition of water, etc.; in the case of the heart, stopping in diastole. From recent experiments of Hogben (*494*) it would appear that the conditions of Ca and K equilibrium among certain invertebrates is the exact reverse of that found in the vertebrate heart. In the heart of crustacea Hogben finds that excess of K causes twitching and eventually rigor. It is evident from this that at present no far-reaching generalization can be made concerning the conditions of ionic equilibrium in all forms of muscle.

The influence of muscle length upon energy liberation. The explanation of *how* increased length of a muscle fibre causes greater liberation of energy presents a difficult problem. If, as seems probable, energy is set free by a wave of increased permeability which permits the interaction of certain ions with a "precursor," the duration of the wave at any one point would determine the amount of energy produced from the resulting interaction. In view of this it is suggestive that the chronaxie of muscle is found to increase with tension (Laugier, unpublished; cf. Fredericq, *340*), as it does in nerves subjected to small stretches (Lapicque et Laugier, *610*). The increased chronaxie would tend to indicate a more prolonged action current (and slower propagation rate, Hieronymus, *468*), and thus more energy. Curare, which also increases the chronaxie of muscle—thus rendering it unstimulable by its normally isochronous nerve impulse (L. et M. Lapicque, *597,607,608*)—is known to increase the heat production of a muscle responding to single shocks by 25 per cent, and Hartree and Hill (*440*), who discovered this remarkable effect, suggest as an explanation of it (p. 410) that curare may "prolong the rise of permeability following the stimulus"—a suggestion which is well in keeping with the alteration in chronaxie produced by this drug. Curare also prolongs the twitch in much the same

way that increasing the initial tension prolongs it (Biedermann, *103*). We may, therefore, consider whether the mechanism of increased energy production in muscle, under tension as well as under the influence of curare, is the enhanced duration of the wave of permeability set up by the stimulus. Are the action currents when tension is high of greater duration than when tension is low?

Unfortunately the string galvanometer, on account of its lag, greatly distorts the true shape of most physiological action currents—most notably

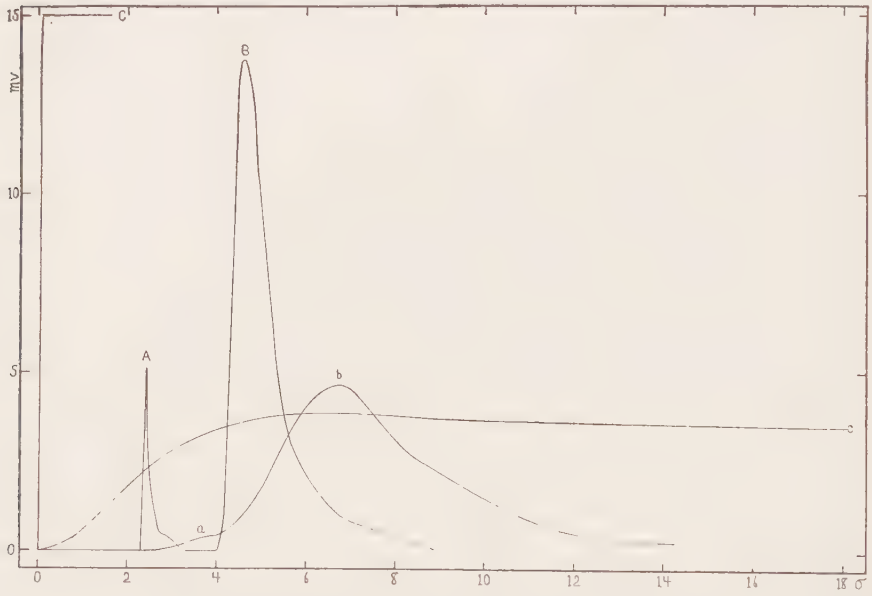

FIG. 88. Gasser and Erlanger's curves in which the shape of the action current of frog's nerve as recorded by the string galvanometer (b) and cathode ray oscillograph (B) respectively are compared. Note also the rectangular calibration curve obtained with the latter instrument (c). (*Amer. Journ. Physiol.*, vol. 62, p. 496, 1922.)

those of medullated nerve and skeletal muscle; and it is extremely difficult, if not impossible, to calculate the true shape of an action current from a string galvanometer record. Gasser and Erlanger (*386*) attempted to do it for the action currents of nerves by mathematical analysis of the string galvanometer curves. The cathode ray oscillograph, however, appeared to them a more convenient alternative for obtaining the result. Gasser and Erlanger's comparisons of cathode ray oscillograph and string galvanometer records are shown in figure 88. For currents of 1σ duration or less

the ordinary string galvanometer acts in reality as a ballistic galvanometer, and it is therefore impossible by means of it to distinguish the *size* (potentials) of the electrical response from its *duration*, when the duration relative to the lag of the instrument is very short. In figure 89 records are shown of the response of a galvanometer string to brief rectangular currents 1 mv. in potential and of the 0.5 1, 2.5, and 4σ duration respectively. Similar responses are obtained with currents of constant duration and varying potential. Davis and Brunswick (*226*) have recently analyzed this point with great throughness in connection with their work in the action current of nerve. Their curves illustrating the effects of varying durations and potentials are shown in figures 90 and 91.

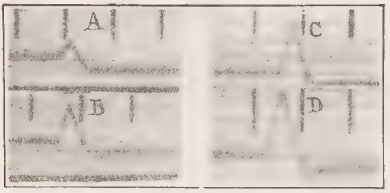

FIG. 89. Showing the responses of the galvanometer string employed in the present research to rectangular currents of constant potential (1 mv.) but varying duration. Delivered by a Lucas spring contact breaker. Tension of the string 11.5 mm. per mv. Time above = 0.02 second (*353*).

A: Duration of current, 0.5σ.
B: Duration of current, 1.0σ.
C: Duration of current, 2.5σ.
D: Duration of current, 4.0σ.

When, therefore, maximal stimuli are delivered to a parallel-fibred muscle and the size of the electrical responses undergoes marked variations with variations of the mechanical conditions of the muscle, a dilemma presents itself: either the electrical response of each individual fibre has altered its potential ("size"), or has altered its duration. If the flow of ions attendant upon the wave of permeability were continuous and not momentary, the potential difference set up would depend upon the degree of polarization of the membrane. de Meyer (*708*) has adduced evidence which indicates that the P.D. on the two sides of the membrane may undergo variation, for he finds that a stretched portion of muscle acquires a potential relatively positive to an unstretched portion. It is possible, that the alteration in size of the action current with tension cannot be attributed wholly to altered duration of the wave; yet in such an experiment as that reported by de Meyer it is extremely difficult to avoid local injury in the stretched portion of the muscle. Since this is the case it is preferable to suspend judgment. As the wave of permeability and its associated action current

are of very short duration, reaching their maximum considerably before the maximum deflection of the string has occurred (Gasser and Erlanger, *287* see above, fig. 88), it is likely that alterations in the apparent size of the galvanometric deflections under the conditions afore-mentioned are due chiefly to alterations in the *duration* of the action current in the individual fibres rather than to alterations in its potential.

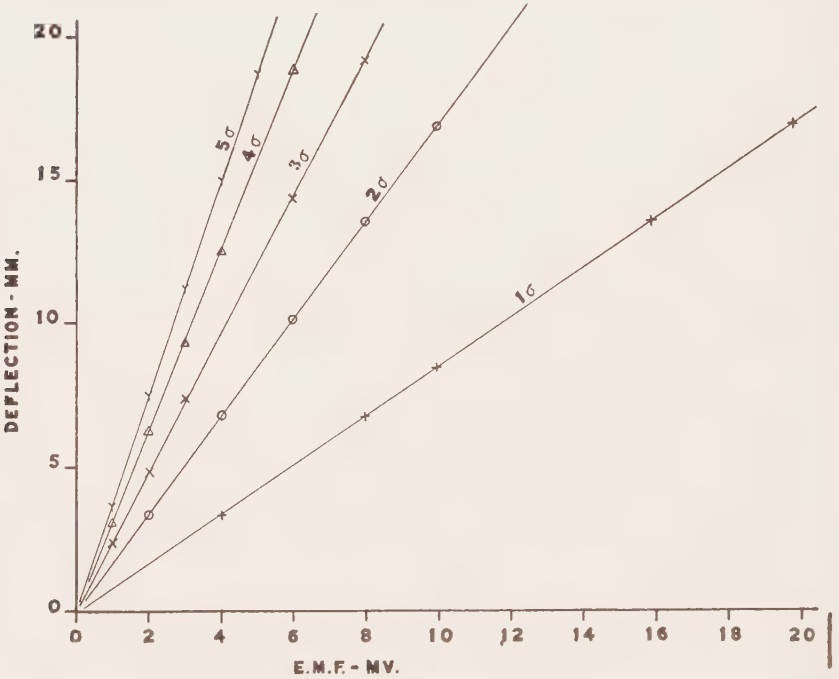

Fig. 90. Calibration of galvanometer. Deflection in millimeters on recording film is plotted against the potential in millivolts applied to the string terminals. The duration of current flow is determined for each series of observations by means of a Lucas pendulum. Each point is the average of two observations. Note the accurate linear relationship between deflection and potential. Resistance constant. Source of current is storage cell and potentiometer. (Davis and Brunswick, *Amer. Journ. Physiol.*, vol. 75, p. 508, 1926.)

There are two important experimental results which support this inference. In the first place, when the temperature of a muscle is lowered, though in a short tetanus the energy liberated—and hence the number of ions which have flowed—is actually less (Hill, *475*, p. 324) the magnitude of the galvanometric responses during the plateau is greatly increased.

Thus in table 11, Chapter VII, it is shown that the plateau electrical responses of gastrocnemius at 23.5° were 10.5 mm. and of the same muscle at 19° under equal initial tension (110 gram) and the same string sensitivity were 14.0 mm. The most likely interpretation of this is that the ions moving more slowly at 19° prolong the wave of permeability and hence increase the size of the electrical response.

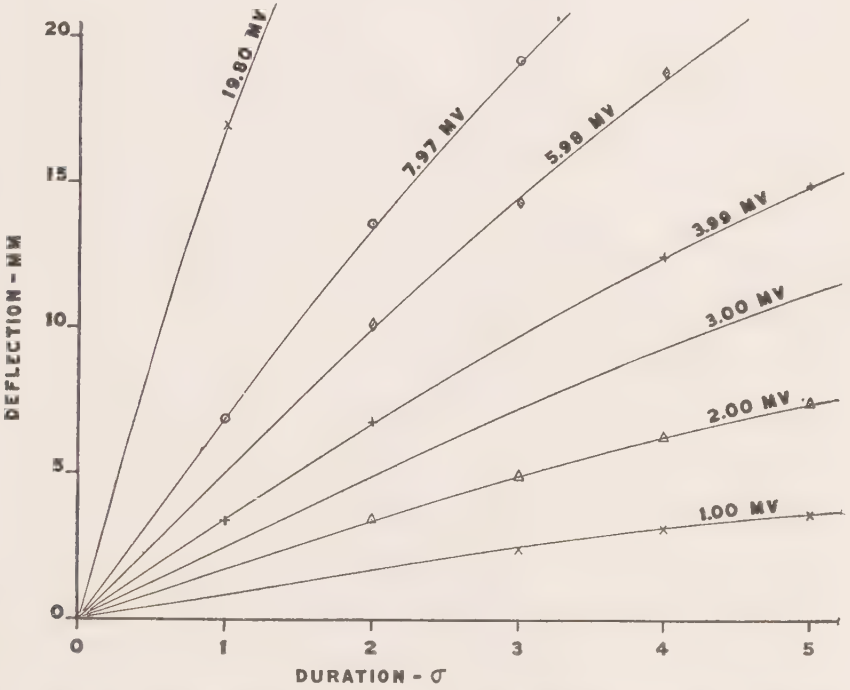

FIG. 91. Diagram showing the influence of current duration on the size of the galvanometer reflection at various potentials. The curvature of the lines is definite, but is slight below 4σ duration and 15 mm. deflection. The deflection is nearly proportional to duration within this range. (Davis and Brunswick, *Amer. Journ. Physiol.*, vol. 75, p. 511, 1926.)

Evidence bearing more directly upon the problem in hand has come from Laugier's experiment (*621*) already mentioned in which it was found that when a muscle is stretched its excitation-time (chronaxie) increases. The duration of the electrical wave necessary to break down the polarized membrane is thus greater in a muscle under tension than in a relaxed muscle. Unfortunately we have no direct evidence of the relation between the time to maximum of the action current and the time to maximum of the optimal

exciting stimulus. A comparison of Lapicque's (see *350; 597, 598 et seq.*) values for the chronaxie of frog's sciatic (0.3 to 0.4σ) with those of Erlanger and Gasser (*287*) on the time to maximum of the action current of the same tissue (0.4 to 0.6σ) leads one to suspect that they are closely allied, but the evidence is as yet insufficient for any far-reaching conclusions and one hopes that this important gap in our knowledge will soon be filled.

The all-or-none principle.[3] The all-or-none principle of muscle fibre response is of fundamental importance to an understanding of the energetics of muscular activity, for it indicates the general type of regulatory mechanism with which we are dealing. If the magnitude of muscular responses varied *continuously* with the intensity of the stimulus, we should be dealing with a mechanism similar in kind to that of an ordinary electrolysis, or to any simple electro-chemical reaction which proceeds to a greater or less extent according as a greater or less amount of energy be expended upon it. However, muscular energetics, as Pratt (*781*, p. 517) has pointed out, are wholly different from this. "If the mechanism of control be regarded as *discontinuous* with the responding system, conceding to the latter an inherent determinate capacity for energy release, it is possible to reinstate the controlling factor as a mechanism for simply utilizing multiples of energy-yielding elements. The excitatory process, in accordance with its access to one or more systems of definite dynamic capacity, will then discharge one or more in strict relation to that access, that is, in strict relation to its own demands." Pratt goes on to say:

> "The alternatives present so great a divergence, on the score of both nature and complexity of mechanism, that the acceptance of one or the other must determine widely different interpretations of contractile phenomena,—gross, microscopic and physi-chemical. For in one case we must recognize the events in sequence as follows:
>
> "Excitation —→ initiation of discharge in responding —→ limitation of magnitude of discharge (massive) in strict conformity to magnitude of excitation (relatively meagre); and in the other,
>
> "Excitation —→ full discharge in every responding system to which the excitatory influence has effective access.
>
> "Thus the first alternative involves, in the same system, initiative plus limitation; the second, initiative without limitation in all systems excited. In the first, control necessitates an inhibition of discharge, quantitatively selective, in a disturbed unstable system; in the second, it requires only that excitation penetrate to each quantum of energy needed in the response."

It may be urged that variation in energy liberation with alterations in the fibre length is contrary to what one would anticipate from the all-or-

[3] Further details concerning the all-or-none principle are given above at the end of the Historical Introduction.

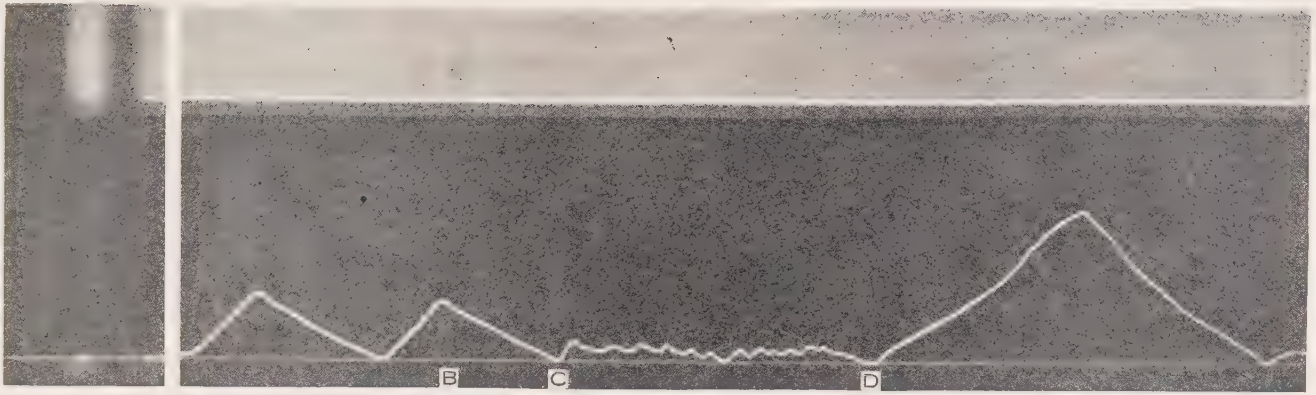

FIG. 92. Another of Pratt and Eisenberger's records showing the discontinuous character of the responses of frog's sartorius as the intensity of stimulation (indicated in the lower curves) is *gradually* altered. Between C and D (upper curves) the threshold was explored and an attempt was made to find some intermediate excursion between the smallest shown and the base line; it could not be found,—it was either that excursion or none at all. Note the abrupt discontinuities in the excursions. (From *Amer. Journ. Physiol.*, vol. 49, p. 31.)

none theory. This is emphatically not the case. The all-or-none principle refers solely to stimulus intensity and it implies merely that in response to any given intensity of stimulation the fibre contracts maximally or not at all. Under given mechanical circumstances it is quite impossible to alter the response of an individual muscle fibre by increasing the strength of stimulus.

There is, however, possibly one reservation to the statement that increasing the strength of the stimulus does not alter the response of an individual fibre, for when far above the threshold, the stimulating current "escapes" and an individual fibre, instead of being excited focally with transmission of the excitation in all directions at the rate of conductivity of the muscle substance, is stimulated instantaneously over a large area. This leads

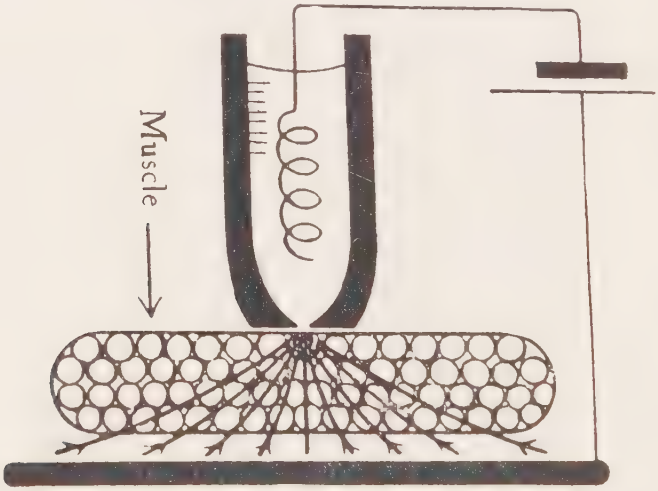

FIG. 93. A diagram of the Pratt pore electrode applied to a muscle. (Adrian, *Arch. Néerland. de Physiol.*, tom. 7, p. 331, 1922.)

to certain slight modifications in the shape of the response of a muscle as a whole (unpublished observations; see also Adrian, *8*, and Bethe and Happel, *97*), but it does not in any way belittle the general significance of the all-or-none principle, since, in the intact animal, muscle fibres are always stimulated focally through the nerve endings.

Adrian (*7*), moreover, has recently (1922) emphasized that since the stimulus and the mechanical response represent the beginning and end of a complex series of processes, the all-or-none, determinate character of the responding system might be due to an all-or-none mechanism interposed at any point along the series of these processes. We have already seen that the electrical response is the first manifestation of activity in the muscle follow-

ing stimulation, and hence it represents one of the first events in the chain of processes responsible for contraction. It is therefore a point of great importance that the electrical response of a single muscle fibre has been found by Adrian to share the all-or-none properties observed by Pratt in the mechanical response of a single muscle fibre (see fig. 92). This Adrian proved by stimulating a sartorius with a pore electrode (fig. 93) and recording the electrical response with an Einthoven galvanometer. As the

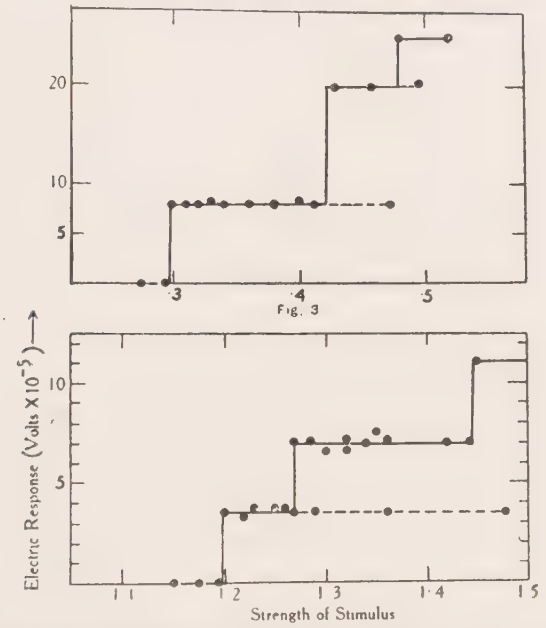

FIG. 94. Adrian's figures illustrating the all-or-none character of the electrical response of skeletal muscle (frog sartorius) as exemplified in two experiments. The abscissae indicate strength of stimulus expressed in arbitrary units, and the ordinates give the excursion of the galvanometer string. Note the abrupt discontinuities. (From *Arch. Néerland. de Physiol.*, vol. 7, p. 332, 1922.)

intensity of stimulation was gradually increased, the recorded electrical response increased in discontinuous steps, as shown in figure 94; moreover, when a step occurred, added fibres were observed microscopically to be brought into activity. "It is therefore highly probable," Adrian concludes, "that there is an all-or-nothing relation between stimulus and electric response just as there is between stimulus and contraction. This agrees with what is known of the electric response of nerve fibre, and it suggests that in muscle the all-or-nothing relation intervenes at an early stage in the

chain of processes which lead up to the contraction." This result has recently (1926) been amply confirmed in nerve by Adrian and Zotterman (*19*, p. 165) in their beautiful analysis of the responses of single proprioceptive end-organs in frog muscle. However strongly an end-organ were stimulated (stretch) the size of the electrical response never varied (see below, p. 357).

In both nerve and muscle a polarized interface has been postulated to account for the electrical variation, and in view of Adrian's findings, it is accordingly legitimate to assume that the all-or-none property of both muscle and nerve is an expression of the properties of this interface.

SUMMARY

The electrical response of all excitable tissues *precedes*, though often by an extraordinarily brief interval (*e.g.*, 0.5σ in mammalian muscle), the beginning of the mechanical response. The electrical response cannot, moreover, be separated from the mechanical response by any means at present known. In other words, whenever an electrical response occurs, a mechanical response is an inevitable sequel. Whether the converse is true, namely, that mechanical responses cannot occur in the absence of electrical responses, though probable, has never been adequately demonstrated. The conclusion has therefore been reached that in normal physiological responses the electrical variation *is* an invariable predecessor of mechanical activity. On the basis of this and other evidence, it is suggested that the action current and the process responsible for energy liberation are governed by the same mechanism.

The size of the electrical response varies with the initial length of the muscle fibre in much the same way that heat liberation varies. Also, the *duration* of any given mechanical response varies with the size of the electrical response. This again suggests that the mechanism of production of the electrical response, and the mechanism controlling initial heat production are one and the same.

The nature of the ionic interchange responsible for the liberation of lactic acid from the precursor is discussed and the possibility that it is due to an alteration in the Ca-K equilibrium is considered.

It is pointed out that the all-or-none principle of fibre activity provides an index of the general type of mechanism involved in the energetics of muscular activity, and that the recognition of this conception is fundamental to an understanding of the contractile process. In the chain of events occurring between application of the stimulus and the appearance of

the mechanical response, an all-or-none relation occurring at any point in the chain of events would determine the character of the response (Adrian). It is therefore a point of great importance that the electrical response, which is the first manifestation of activity, is itself all-or-none in character. Since the electrical response appears to be produced by a polarized interface in the tissue, it therefore follows that the properties of this interface would give to the muscle fibre, as a whole, its all-or-none characteristics.

CHAPTER IX

The Contractile Process; Résumé and Conclusions

Internal "viscosity" and the elastic body hypothesis

Since the days of Weber (*1033*), a muscle has generally been looked upon as an elastic body which assumes new elastic properties on excitation. Using this hypothesis, Hill (*473*, 1913) originally assumed that the work which a muscle is capable of performing is proportional to its length, l, and the tension, T, which it exerts during isometric contraction. He observed by constructing a tension-length diagram (*473*, p. 450) that the theoretical maximum of work is equal to Tl multiplied by a constant factor (= one-sixth in the case of a strip of parallel-fibred muscle, Mashimo, *692*). An attempt was then made to correlate $Tl/6$ with heat. It was found that in isometric contraction the initial potential energy liberated as heat is approximately equal to that calculated on the basis of $Tl/6$. In other words, the whole of the potential energy in a twitch appeared to be converted into external work, and the efficiency of the muscle on this basis was thus of the order of 100 per cent (excluding recovery heat). When, however, the muscle was actually permitted to shorten and to lift a weight it was found unable even to approximate its theoretical maximum of mechanical work. As Hill pointed out, either the elastic hypothesis was incorrect or some hitherto undiscovered factor prevented the transformation of elastic energy into work.

This discrepancy led to a series of investigations of surpassing interest and importance. Hartree and Hill (*480*) found that rapid stretching or releasing of a muscle was accompanied by thermodynamic changes of temperature akin to those first observed in other substances by Kelvin. When the muscle was stretched a large irreversible production of heat resulted, and it was suspected on the basis of these results that the reason why a muscle is incapable of transforming its elastic energy into work is that the frictional and viscous resistances associated with the shortening process cause a large irreversible dissipation of energy. The further development of these investigations in the hands of Hill (*476*, *485*, *479a*), Lupton (*669*), and Gasser and Hill (*390*) has recently been described in Hill's monograph (*479*) and need not be repeated here. Several of Gasser and Hill's experiments, however, may be mentioned.

They found (as had Fick, *303*) that an inertia is the optimal type of load for obtaining work, *i.e.*, the muscle must shorten slowly and to a small extent. The maximum of work was obtained when contracting against an inertia device having a mass which the muscle could just move, and it was found that the work decreased continuously as the speed of shortening increased owing to the use of lighter weights. From this they argue that the

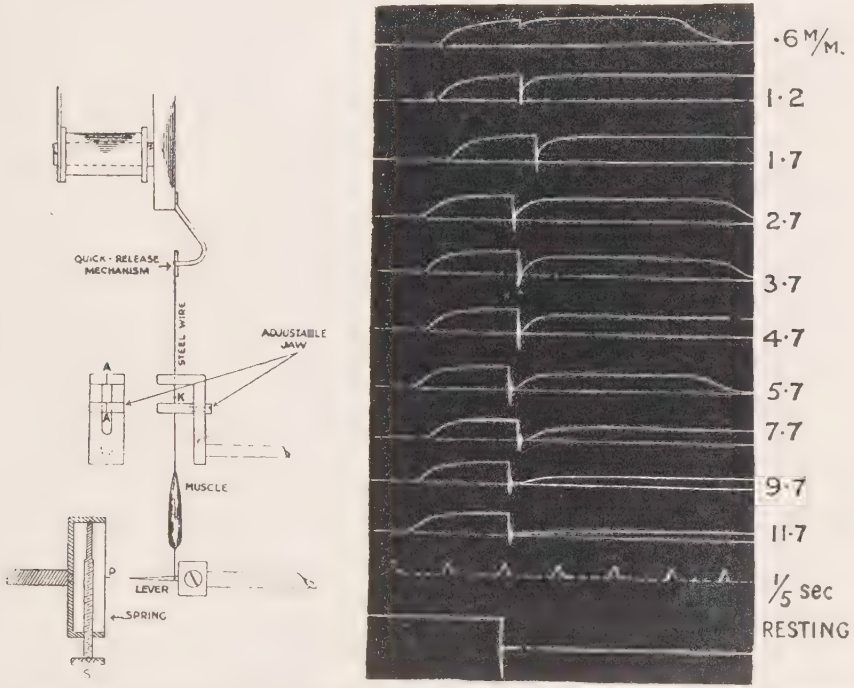

FIG. 95. Isolated sartorius of the frog released during the plateau of tetanic responses by varying amounts, indicated at the right of the figure. Note that the redevelopment of tension after release, follows a curve similar to that of the original tension curve. (From Gasser and Hill, *Proc. Roy. Soc.*, vol. 96B, p. 405, 1924.)

force exerted by a muscle decreases as the speed of shortening increases.[1] Gasser and Hill's experiments were further corroborated by another series of observations in which the muscle was stretched or released during activity.

[1] The same conclusion was reached by Hill in his analysis of the rate of movement of human arm muscles (*476*). As this result is thus corroborated on excised muscle it indicates that the experiments on human muscle were probably not vitiated by intervention of proprioceptive influence.

They observed that when a muscle is released at the height of a tetanic response to a slightly shorter length, it does not immediately take up the tension anticipated on the basis of a tension-length diagram; on the contrary, the tension falls quickly toward zero and there follows a slow redevelopment on a curve similar to that of the original tension development (fig. 95). This is interpreted as due to the fact that the contractile elements, in order to regain the tension of the new length, must overcome the internal frictional forces which they had originally to overcome when

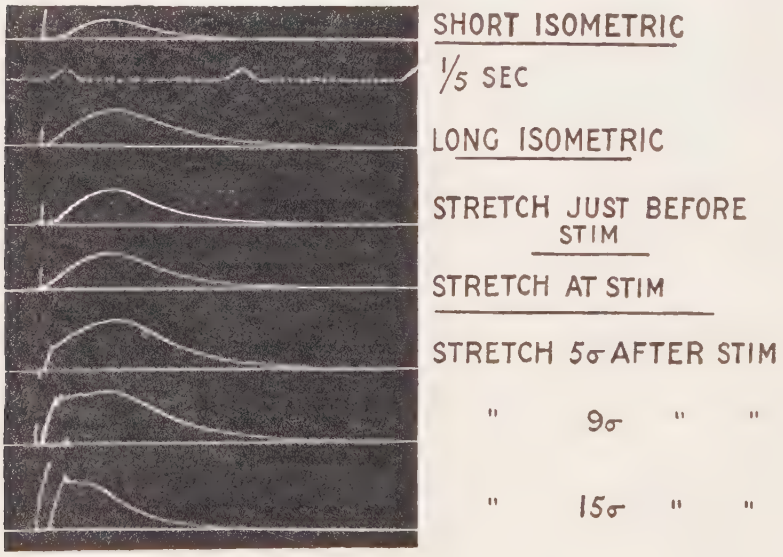

FIG. 96. Records showing the effect, on the tension developed, of stretching a frog's sartorius muscle at various moments before and during an isometric twitch. Note that the greatest tension is developed at 5σ after the stimulus; the stretch thus falls during the period of rigidity, as elucidated in Chapter II. (From Gasser and Hill, *Proc. Roy. Soc.*, vol. 96B, p. 431, 1924.)

the tetanus was first developed. To prove the correctness of this interpretation, they undertook experiments in which the muscle was stretched at various intervals following stimulation. They found that it offered the most resistance to the stretching force at approximately 5σ after the stimulus (fig. 96). The internal stress, in other words, is probably greatest at this point but is unable to show itself owing to a "viscous" impediment. It will be seen that these observations harmonize with the existence of a period of rigidity previous to shortening which was described in Chapter II of this

monograph. The period of rigidity has been interpreted as one during which the muscle is prevented from shortening, probably because of internal friction. When stretched in this initial phase of activity the muscle opposes extension with greater force than at any other period.

Hill (*479a*) has emphasized that the conception of muscle "viscosity" must not be interpreted too literally, for the term as used obviously includes phenomena not strictly comparable to simple physical viscosity. "It would seem that the development of contraction is due to the formation of some molecular pattern in the muscle fibre, to some process analogous to crystallization; when the muscle is released its tension can be developed again only by the rearrangement of its elements in a "crystal" of the same molecular pattern, but of different external shape" (p. 114). "The equilibrium condition is not always instantaneously reached in a film of molecules packed upon a surface, nor probably is the spatial lattice of a crystalline liquid formed in a moment . . . . In some such way, rather than by invoking simple physical viscosity, I think one must proceed. Viscosity in a sense it is: not gross, but molecular. . . . This slowness of attainment of a final state, involving molecular "viscosity," is a common property of many physico-chemical systems" (p. 103).

The stretching experiments of Gasser and Hill led them to postulate the existence of an internal "fundamental process" as distinguished from the external manifestation of that process (the development of mechanical tension). The fundamental process, according to their conception, rises rapidly to a maximum, while the external process (mechanical change) lags behind. In Chapter IV evidence of a different nature has been given supporting the same conclusion. The characteristics of the "fundamental" processes were investigated and its course determined by the effect which it was capable of producing upon a second response. It was found to run in its initial stages a course similar to that postulated by Gasser and Hill. The mechanical manifestation is, however, characterized by an abrupt discontinuity (the "angle") which was not recognized at the time of Gasser and Hill's work. Are we to assume that this reflects a similar discontinuity in the fundamental process, or is it to be regarded as an idiosyncrasy of the external process?

To consider this point it will be useful to restate the evidence concerning the nature of the "angle." The properties of an unfatigued muscle during the period (relaxation) following the "angle" have been shown by three different methods to differ from its properties during the period preceding the "angle." (1) The *rate* of relaxation of the muscle is nearly constant at any given temperature. This, together with its concave shape, suggests a passive process as contrasted with the clearly active process characteristic of the period preceding the "angle." (2) A first response at any point preceding the "angle" is capable of enhancing the duration of a second

response, owing presumably to the incomplete dissipation of the ions liberated in the course of response I. After the "angle," the power of augmentation ceases. Finally, (3) the temperature coefficient (10°) of the rate of decline of tension is only 1.3 to 1.4, while the coefficient of the kinetic phase of the twitch lies between 2.0 and 2.1. Similar values were obtained for the corresponding phases of short tetani (Chapter V). This again suggests that the declining tension is a purely passive physical process. In other words, the "fundamental" process—whatever it may be—ceases at the "angle," and the muscle as a whole, being unable to follow the abrupt ionic alterations, returns to its resting condition as rapidly as internal forces permit. This will be referred to again when discussing Garner's theory of contraction.

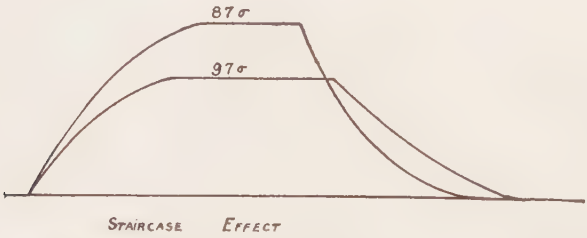

Fig. 97. Staircase effect. Two successive twitches plotted on the same coördinates. The lower one, whose duration was 97σ, was taken under exactly the same mechanical conditions as the upper one but was the first response after a prolonged rest. The area of this one is 808 (97 × 7.3). The upper one, whose duration was 87σ, was taken two minutes later, the muscle having been stimulated in the interval by a brief tetanus. The area of the upper twitch is 870 (87 × 10) (*361*).

The "staircase" effect. The conception of internal "viscosity," together with the observations on the effect of shortening during contraction, throw light upon the "staircase" effect. We have found (Chapter III) that when a muscle executes a twitch after a prolonged rest the mechanical response is marked prolonged, as measured to the "angle," while the tension developed, as is well known, is considerably smaller than in ensuing contractions. The increased duration suggests a greater limitation of the degree of freedom for shortening of the contractile elements in early than in later responses. This has led to the belief (*361*) that after a prolonged rest the muscle becomes, as it were, "set," and as a result, in the first few responses the contractile elements encounter greater internal resistance than after the muscle has become "limbered up." In figure 97 two responses are shown, one taken after a rest and the other from the same preparation after a short tetanus. Whether there is a secondary facilitating effect

resulting from the presence of H ions, as Mines suggested (*717*), is not known. However, it may be recalled that the hydrogen ion theory has been severely criticized by Adrian (*6*), since he found the effect in cardiac muscle not marked when an alkaline perfusate was used. The "viscous effect" is probably sufficient to account both for the altered duration and the increased tension in successive responses. Consequently the hydrogen ion theory may prove unnecessary to account for the phenomenon of the staircase.

THE CONTRACTILE PROCESS

It can be said with truth that no theory of muscular contraction yet offered has proved satisfactory. Those which have been based upon the structure of the muscle fibre (see *867*; also *674*, *981*), though often suggestive, have not been able fully to account for many features of muscular physiology. There are, however, certain outstanding facts which the structural theories of muscular contraction make it necessary for us to recognize.

The structure of muscle fibres. The structure of skeletal muscle fibres may be ranked among the most perplexing of histological problems, for the researches of many distinguished microscopists have not served to make the matter clear. An attitude of resolute agnosticism is therefore the duty of anyone who does not hold first-hand information. With one or two notable exceptions, each histologist who has investigated the problem has elaborated a new theory of contraction, yet those who have made the most important recent advances in muscle physiology have disregarded minute structure entirely and have looked upon the muscle simply as a machine for the transformation of energy, noting only what goes into it and what comes out. The thermodynamic attitude is indeed useful on account of its very lack of specificity. Polarized membranes are postulated and liquid crystals assumed to explain observed phenomena, and such postulations pass unchallenged so long as they remain physical or thermodynamic necessities, without being correlated with histological structure. However this may be, the inquiring mind of the student demands tangible structures with which to associate polarized interfaces. Are we therefore to remain hopeful that the histology of the future will provide us with a knowledge of the situation of the physico-chemical surfaces with which all physiologists are now so deeply concerned, or must we resign ourselves to Rutherford's (*831*) view that the "structure of the fibril is beyond the reach of the microscope so that the secret of contraction will ever remain hidden?" When one seeks the histological situation of the polarized membrane responsible for the electrical change one finds at present nothing but vague possibilities.

A skeletal muscle is made up of fibres varying in diameter from 10 to 70μ, those of the frog's sartorius being about 40μ. Each fibre is divided longitudinally into *sarcostyles* which lie in the fluid sarcoplasm of the fibre. Sarcostyles are divided transversely by Krause's membrane into segments known as *sarcomeres* or "sarcous elements." Sharpey-Schafer (*863*) finds that when sarcostyles are separated from sarcoplasm they are still able to

contract. Most physiologists in consequence of this look upon the sarcostyle as the ultimate contractile unit of the fibre. Great difference of opinion, however, exists as to the way in which a sarcostyle shortens, for each of the segments has a complex structure. In the region of Krause's membrane is a light area which is singly refractive to polarized light and in the middle is a dark area of double refraction. When contraction occurs the doubly refracting regions are believed by some authors to increase at the expense of the singly refracting regions. Tiegs (*980*) describes within the individual sarcomeres an actual passage of doubly refracting fluid through ultramicroscopic channels during contraction.[2] The residual hyaloplasm passes, according to this author, from the central doubly refracting region to the region of Krause's membrane at either end of the sarcomere, but inasmuch as the dimensions of the sarcomere are of the order of 1μ and sometimes less, one must be hesitant in accepting microscopic interpretations, as they are so notoriously influenced by subjective impressions. Tiegs (*980*) has also made another important observation. He points out that when a single muscle fibre is carefully focussed under the microscope each successive transverse striation of Krause is continuous with the next striation so that it really forms a continuous spiral band or helicoid extending throughout the length and breadth of the fibre (see fig. 76, Chapter VI). The individual sarcomeres are, according to this conception, arranged in layers between the successive turns of the spiral membrane. It is interesting that Leeuwenhoek (*627*) in an early description of muscle fibres referred to the spiral thread wound around the outside of the "fibrillae" (or fibres, as we should now call them). Tiegs is inclined toward the opinion that the excitatory disturbance travels along this helicoid. He points out that when the proper dimensional constants for the muscle fibre of the frog are substituted in the formula giving the actual distance that the excitatory disturbance would have to travel if it passed along this spiral, it is found that the rate of transmission is the same in muscle as in nerve, *i.e.*, 30 m. per second. It is difficult to pass judgment upon this interesting suggestion in the present state of knowledge. It is, of course, from the physico-chemical standpoint unnecessary to assume that an interface necessarily means a morphological structure, and it may be pointed out in this connection that Krause's membrane, though clearly passing across the interfibrillar sarcoplasmic spaces, does not hinder the passage of an object imbedded in the sarcoplasm; for Kühne (*567*, *568*) was fortunate enough one day to find a minute nematode swimming up and down an individual muscle fibre, and he observed that it passed from one segment of the fibre to the next quite oblivious of the existence of Krause's membrane which apparently reformed itself immediately the animal had passed through, very much as a soap-bubble closes after a needle has dropped through it. Most investigators, however, have tacitly assumed that the membrane responsible for the electrical change passes longitudinally. If it were merely a membrane around the whole surface of the fibre it is difficult to understand how it could regulate the energy supply of sarcostyles far within the centre of the fibre, and if it turns out to be longitudinal (instead of being a helicoid) it is more likely that the longitudinal interface will be one associated with each individual sarcostyle. The recent development by Chambers (*192*) and others of the technique of micro-dissection lends great promise that the minute anatomy of muscles may be worked out in more detail. He has already observed that the sarcolemma is a well-defined membrane resistant to stretching. When it is removed from the surface of the fibre the

[2] As Tiegs' papers are somewhat inaccessible, I have abstracted their contents in some length in *Physiological Abstracts*, vol. 9, pp. 302–305.

remainder of the fibre retains its integrity; in other words, the sarcolemma according to this observation is to be looked upon merely as a protecting or insulating sheath, which is in keeping with previous conceptions.

The theory of contraction outlined by Hartree and Hill may be given in their own words (*439*, pp. 139–140): "Let us suppose that contraction is due to the appearance of a chemical body B (lactic acid) in the neighbourhood of certain surfaces or colloidal networks of the muscle and that in relaxation B is removed from the seat of its action by some physical or chemical means (*e.g.*, neutralisation). Let us suppose next that B is produced from some chemical body A, of which there is a large supply in the muscle; these hypotheses are not *ad hoc*, they are generalizations from previous work on the lactic acid and heat production of muscle. We may suppose that the equilibrium exists inside some narrow space whose boundaries are impermeable to the active agent B (lactic acid). A shock causes in these boundaries a momentary rise of permeability to B, this rise of permeability being manifested by the electric change: B immediately passes out: since outside it causes a rise of tension in the colloidal system there, and the mechanical response ensues. Relaxation is then produced by the neutralization removal, or combination of B, with an evolution of heat and then in the presence of oxygen B is removed by oxidation, or by restoration to its previous position inside the 'reservoir,' or by both." Such a scheme of the contractile process is sufficiently elastic to admit of wide modification in detail. It makes no demands upon the structural mechanism, but when the latter has been worked out satisfactorily there can be little doubt but that this thermodynamic picture of the process will then find an adequate setting. Further details concerning the contractile process have recently been suggested by Garner (of A. V. Hill's laboratory).

Garner's liquid crystal hypothesis. Engelmann was the first to emphasize (*281*) that contractility is always associated with double refraction,—a thesis amplified and extended to great advantage by Vlès (*1003*). Garner (*378*) has made this the basis of a theory of muscular contraction which appears to offer greater promise than any that have hitherto been put forward. Double refraction gives evidence of molecular orientation and the doubly refracting areas correspond morphologically with portions of the sarcostyles. The fluid sarcoplasm surrounding the sarcostyles is singly refracting.

Garner has put forward cogent reasons for believing that certain segments of the sarcostyles of a muscle are in reality liquid crystals of protein,[3] fatty

[3] Recently Gorter and Grendel (*Nature*, vol. 117, p. 552, 1926) have pointed out that small amounts of lactic acid have a marked influence upon the degree of spreading of

acid, lecithin, cholesteryl, or some body of this class (*379*). He draws attention to the recent X-ray analyses of the structure of liquid crystals by Friedel, Piper and Grindley who have found that certain groups of the crystals are arranged in straight chains, each molecule of which is normal to the bounding surfaces of the liquid, and that the molecules themselves are situated at greater distances from each other than in the corresponding solid crystals of these substances. Garner then offers the following reasons why when acid becomes concentrated at the surface of a liquid crystal having this arrangement, the individual molecules of the crystal will come closer together and thus cause shortening of the crystal itself. (1) Doubly refracting liquids possess a looser structure than when solid, and con-

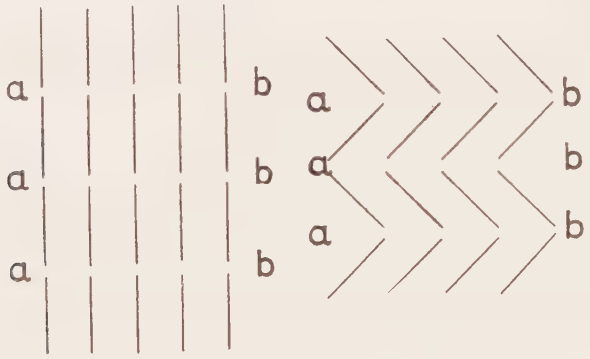

FIG. 98. Garner's representation of the differences in spatial arrangement between the esters of aliphatic acid molecules (left) and the free aliphatic acid. A change such as this may occur in the postulated liquid crystal surfaces of the sarcostyles in muscle during activity, and thus account for shortening. (Garner, *Proc. Roy. Soc.*, vol. 99B, p. 44, 1925.)

sequently a change from the crystalline liquid into the solid state will cause shortening in the direction of the optical axis. (2) Chemical changes occurring in the terminal groups, as Langmuir and others have shown, result in a decrease in the magnitude of the individual molecule and hence a diminution in the crystal as a whole. (3) Change in the chemical nature

extracts of muscle protein upon a water surface. Thus a change in *p*H of 6.4 to 4.8 causes a threefold diminution in surface area. The quantity of lactic acid necessary to bring about such an alteration is of the same order of magnitude as that produced during a single contraction (0.031 mg. per gram of muscle). These authors also point out that this amount of lactic acid would not be sufficient to hydrogenate a lecithin-kephalin surface, which probably excludes the theory that the contractile surfaces in muscle are lipoidal in nature.

of the terminal group often causes a re-orientation of the molecules themselves. This is indicated diagrammatically in figure 98.

With this as a basis, Garner has elaborated a model of a contractile segment of a sarcostyle (fig. 99). He has postulated the existence of two membranes, separated from each other by the width of several molecules. These, for convenience, are referred to as membranes I and II. Garner concerns himself only with the contractile mechanism, and does not consider the excitatory mechanism by which energy is released, suggesting only that the

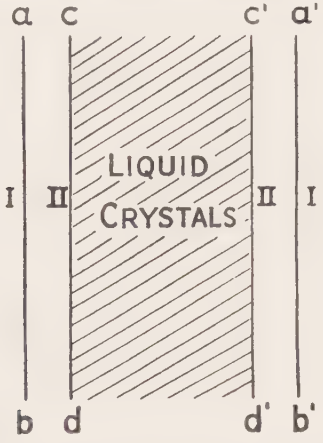

FIG. 99. A diagram of the "membranes" postulated by Garner to account for the phenomena of muscular contraction. Membrane I is an interface which by hypothesis exists a few molecular layers distant from Membrane II, which represents the surface of the liquid crystal (sarcostyle). Membrane I is that along which the lactic acid molecules become oriented so as to influence Membrane II. (Garner, *Proc. Roy. Soc.*, vol. 99B, p. 48, 1925.)

Lillie model of a polarized interface is probably adequate to account for excitation. Liberation of lactic acid,—however, it comes about,—leads to the formation of a monomolecular layer of lactic acid molecules (membrane I). Since this membrane is, by hypothesis, only several molecular layers distant from the liquid crystal surface (membrane II) the monomolecular layer of acid can readily influence that surface, and in this way bring about shortening. When the lactic acid molecules at membrane I become dissipated by buffer action, relaxation occurs.

Garner then considers the consequences of alterations in the extent of surface resulting from changes of form of the muscle as a whole. He points out that changes occurring before and during contraction will affect the concentration of the bodies reacting at the fibre interfaces. Thus,

shortening of the fibre will lead to a greater interfacial concentration, which will in turn lead to an acceleration of any chemical reactions taking place at that interface. Lengthening, on the other hand, will have the reverse effect, owing to diminution of the concentration of ions at the interface. These *a priori* considerations throw light upon observations which had been recorded in the previous chapters relating to the *duration* of the mechanical responses at different lengths.

If, according to Hartree and Hill's hypothesis, one assumes a polarized interface (*not* to be confused with Garner's Membrane I) which controls the liberation of lactic acid, it is clear, from the evidence presented in the last chapter, that we are justified in regarding such a postulated surface as identical with the membrane responsible for the electrical variation. When the muscle is extended, the concentration of reacting ions at this interface becomes less, and this leads presumably to a more prolonged alteration in the permeability of the interface when excitation occurs. As the muscle shortens, the concentration of reacting bodies becomes greater and the duration of the change as a result is shorter. This gives a useful working hypothesis of the mechanism of energy release in contractile tissues. Further evidence supporting it has been alluded to in the previous chapter.

Garner's membranes I and II. The prediction that shortening affects the rate of reaction of the bodies concentrated at membranes I and II, completely harmonizes with the observations recorded in Chapter III on the effect of shortening during an isometric twitch. We have seen that when a twitch is recorded under perfect isometric conditions the duration of the twitch is at its maximum. In other words, the bodies reacting at the contractile interface (membrane II) are dissipated more slowly than when shortening occurs during the twitch. On the basis of Garner's suggestion this is interpretable on the view that the greater concentration of bodies occurring as a result of shortening has led to an acceleration of the reaction.

We have, therefore, to distinguish between two effects: (1) The greater duration occasioned by increasing the *initial* length which, as Garner points out, is probably a combination of effects, (*a*) of the increased duration of the wave of permeability and (*b*) the greater surface offered by membrane II. (2) The altered duration of the twitch when varying degrees of shortening are permitted during its course appears to be due only to alteration at membranes I and II, for according to the hypothesis after the electrical response has passed away the excitation membrane ceases to function.

THE FENN EFFECT

Garner's deductions appear to throw light upon the perplexing phenomenon described by Fenn (*298*, *299*). Fenn observed that when a muscle shortens it liberates in addition to its isometric heat an excess of energy which is roughly proportional to the work performed as a result of shortening. He finds that when lifting a weight the *total* energy liberated as heat is approximately the same as that liberated in an isometric contraction; consequently an extra amount of heat has been liberated which is equivalent to the work done in lifting the weight. The result has been amply confirmed by Hartree's (*437*) recent investigation. Now, we have the observation that when a muscle shortens, the duration of its contraction as compared with its isometric duration diminishes. Garner and Hill both emphasize that as soon as lactic acid is liberated the reversible nature of the reaction must cause a portion of the lactic acid to become reformed into glycogen as soon as it is released. The briefer duration of the response when shortening occurs presumably provides less opportunity for the reversal of the reaction, and consequently more of the lactic acid is neutralized at the surface when there is shortening than in an isometric contraction. Along some such lines as these it seems possible to account for Fenn's observation that more energy is liberated when shortening occurs than when it does not (*361*).

Whether or not the liquid crystal theory can be utilized in accounting for the "angle" remains an open question. If, as Garner believes, a monomolecular film of lactic acid becomes concentrated near the surface of membrane II, it is conceivable that the dissolution of the film would occur instantaneously, as the flow of ions from the source ceases to be sufficiently great to maintain the integrity of the film. Abrupt phase reversals in such a heterogeneous system as the muscle would not be an unusual occurrence in view of the sudden reversals which Clowes (*196*) has described in other forms of protoplasm. The question of the ultimate causation of the "angle" must of course be left open, but that it represents a fundamental discontinuity in the contractile process must be recognized. The difference in the temperature coefficient of the two phases of the twitch is sufficient evidence for this conclusion quite apart from a mechanical evidence of the discontinuity.

It is difficult to understand why in Garner's theory it is necessary to assume that lactic acid molecules cannot activate a liquid crystal surface without forming a continuous monomolecular film. The essence of Garner's theory is that a temporary chemical union occurs between the surface molecules of the liquid crystals and the lactic acid molecules. This being the case, it would seem possible for the effect to occur to a greater or less extent according as a greater or less number of molecules combined stoichiometrically with a

corresponding number of molecules on the surface of the crystal. Hill has recently made an ingenious calculation of the area of a monomolecular film of the lactic acid which is liberated within a fibre 1 cm. long when developing a force of one dyne (*478*). This was found to be 1.46×10^{-11} grams which is equivalent to approximately 10^{11} molecules which, when spread into a film, would have an area of 2.1×10^{-4} sq. cm. Hill points out that if the mechanical response of muscle were due solely to an alteration in the surface tension caused by a film of lactic acid, the coefficient of surface tension would have to be of the order of 4,800 dynes per square centimeter, or about 230 times the tension of a water-olive-oil interface. A calculation was also made of the probable area of the ultimate muscle fibrils (sarcostyles), and it was found that their area was approximately 44 times greater than that of a monomolecular film of lactic acid liberated in a maximal contraction. Though the initial assumptions made in the calculation of the internal surface of the contractile element are far from secure, the divergence between the area of the lactic acid film and the area of the contractile surfaces appears to be sufficiently great to preclude the possibility of the simple surface-tension hypothesis of contraction put forward by Bernstein (*92*). On *a priori* grounds it would of course be surprising if the area of a monomolecular film of lactic acid were actually equal to the surface offered by the contractile elements, for if this were the case it would be difficult to account for the differing magnitude of contraction as the lactic acid liberation becomes increased. Thus, when two stimuli follow each other at a brief interval (*e.g.*, 5σ), a summation occurs not only of duration but also of tension developed. It is obvious that under these circumstances the lactic acid liberated not only persists in activity for a greater length of time but produces greater tension. In other words, the extent of liquid crystal surface affected must be greater than for a single stimulus. If the formation of a film of lactic acid is necessary to bring about shortening there is no reason for rejecting the possibility that the film may be confined to a small portion of the available surface of the contractile elements. When more lactic acid is liberated the extent of the surface so covered simply becomes greater.

As a result of Bernstein's (*92*) theory it is commonly held that tension development in muscle is characterized by a negative temperature coefficient because contraction is a surface tension phenomenon (*e. g.*, *59*, p. 448). However, Hill (*478*) has demonstrated the inadequacy of this explanation, since, among other reasons, heat/tension ratios are the same at all temperatures. Moreover, W. Amberson (unpublished; personal communication) has proved by an accurate isometric technique that the tension development of sartorius, in point of fact, has *not* a negative temperature coefficient.

SUMMARY

It will now be permissible to summarize the chief features of the foregoing theories concerning contraction. Let it be clearly understood that the matters discussed in this chapter are largely in the nature of working hypotheses and are not urged as accepted dogma. The facts of muscle physiology are set forth in Chapters I to VIII, and from these a judicious

reader will form his own conclusions; the present chapter contains one interpretation of existing observations, and will have achieved its purpose if it serves to stimulate further investigation.

A wave of permeability with its attendant potential difference of characteristic duration passes down the motor nerve and leads to a hypolemmal concentration of ions in the region of the motor end-plate. This ionic concentration, either directly or mediately through some as yet unknown agent, causes a wave of permeability to sweep along individual muscle fibres. The morphological path along which the excitatory wave travels in the muscle is at present unknown, but we are justified in believing that it lies in close structural contiguity with the sarcostyles. The ionic interchange resulting from the wave of excitation is responsible for the action current as well as for the liberation of lactic acid. Lactic acid apparently causes contraction, and it probably does so through hydrogenation of the regularly arranged surface molecules of the sarcostyle, the acid being presumably liberated within the sarcoplasm.

When the length of the muscle fibre is altered, either before excitation or during contraction, the three phases of activity,—the electrical, mechanical and thermal—undergo parallel modifications. With increased length the electrical, mechanical and thermal responses all increase, up to a certain point. This may be interpreted, according to Garner's hypothesis, as due to the diminished concentration of reacting bodies at the fibre membranes with the greater surface afforded by the increased length of the fibres. Various features of the mechanical response of skeletal muscle, such as the rate of development and the shape of the curve of relaxation, the response to stretch, etc., are to be accounted for most readily by the conception that the contractile elements are possessed of high molecular "viscosity," and in the process of shortening they must of necessity overcome this frictional impediment. When a "quantum" of lactic acid is liberated by a given stimulus it surrounds the sensitive contractile interfaces, possibly as a monomolecular film, and when the concentration of acid ions sinks below a certain threshold value an abrupt phase reversal appears to occur which leads to the sudden cessation of activity. This suggests itself as the cause of the "angle" in the mechanical response. The shape of the ensuing curve of relaxation, according to this interpretation, is determined by the internal molecular "viscous" forces of the muscle. Such in very rough outline is a tentative picture of the events accompanying contraction.

PART II

The Nature of the Integrative Control Exerted by the Central Nervous System upon Skeletal Muscle Fibres in the Performance of Movements and in the Maintenance of Postures

CHAPTER X

The Principles of Interpretation of Mechanical and Electrical Records of Reflex Responses

We have seen in the previous chapters that a low point of inflection and a sharp "angle" are mechanical features denoting synchronous commencement and cessation of activity of individual fibres participating in a given contractile response. It was found that these features characterize twitches as well as short tetani of parallel-fibred muscles. Advantage will accordingly be taken of these features of the activity of individual fibres in interpreting reflex responses. Especially useful for this purpose is the abrupt discontinuity or "angle" in each response. The outline which follows will give the principles of analysis and interpretation of various reflexes, but it will, to a certain extent, anticipate the evidence upon which the methods of analysis rest. This evidence will appear fully in the course of later chapters.

From the mechanical record, one can determine:

1. Single volley. Whether a given reflex response is a twitch or a short tetanus, *i.e.*, whether it is produced by a single or a repetitive volley of motor nerve impulses. It will be remembered that the duration of a twitch (or a tetanus) refers to the interval between the beginning of the (first) electrical response and the "angle" of the mechanical response. Now the *duration* of a maximal motor twitch at any given initial passive stretch of the muscle is practically constant, *i.e.*, *it is constant* within 2 to 3 per cent for the skeletal (white) muscle fibres of the cat. At a low initial tension the duration may be as brief as 34σ,[1] and at a high initial tension as great as 42σ, being approximately 38σ for the rectus femoris of a two kilo cat at 100 grams initial stretch and temperature of 35°. Therefore, if the duration of a reflex mechanical response is of this order of magnitude when the muscle is at this temperature and initial stretch, it is then clearly produced by a single volley of motor nerve impulses (fig. 100 A). If, however, a tetanus occurred produced by *two* volleys of motor nerve impulses separated by a brief interval of time (*e.g.*, 6σ), the duration of the mechanical response would be approximately 50 per cent greater than that of a single twitch, *i.e.*,

[1] $1\sigma = 0.001$ second.

55 to 60σ. No response can occur having an intermediate duration (*e.g.*, 47σ) under the same conditions of temperature and initial tension. In other words, the considerable enhancement of the *duration* of a double response above that of a single response can leave no doubt as to their distinction. It may be noted in passing that the duration of the response provides evidence as to the existence of ("wave") summation, whether responses are maximal or not.

2. Single asynchronous volleys. If, as judged by the duration of the mechanical record, a given reflex response is produced by a single volley of nerve impulses, one may then determine by the *configuration* of the mechanical record whether the volley is synchronous, *i.e.*, whether all of the nerve impulses reach their respective fibres at the same, or at approximately the same instant. If not synchronous (fig. 100 B), (*a*) the point of inflection of the mechanical ascent will be higher than that of a (synchronous) motor nerve twitch, (*b*) the total tension developed will be somewhat less, (*c*) the terminal "angle" will be less precise, (*d*) the duration of the response will be slightly greater than that of a twitch, but much less than that of a double response, and (*e*) the curve of relaxation will have an initial "nose" (convexity) and the concave portion will be less steep than the corresponding part of a twitch. Asynchronism of a single volley, as Forbes and Gregg (*320*) have pointed out, is also reflected in the behaviour of electrical response, it being (*a*) more spread out than that of a twitch (greater duration), (*b*) possessed of a higher point of inflection (*365*), and (*c*) being of considerably less amplitude for a corresponding tension-development. For example, in Ballif, Fulton and Liddell's (*48*) analysis of the knee-jerk of spinal and decerebrate animals, they found that if the knee-jerk of a decerebrate animal in which four hundred gm. tension was developed, were compared with a motor twitch of the same muscle, in which the same amount of tension was developed, the electrical response of the decerebrate jerk might be less than half the amplitude of the electrical response of the motor twitch, and in the former case it always tended to be slightly more spread out than in the twitch. This was interpreted as due to the electrical responses of the individual units occurring in sequence and in that way tending to interfere with each other, as Lewis (*629*) has described in the case of heart muscle.

3. Tetani. The mechanical record, by virtue of its duration, reveals the presence of repetitive responses of individual muscle units, even when, owing to the asynchronous character of the repetition there is little or no recordable electrical manifestation of the repetitive "firing" of the individual elements (fig. 100 C, synchronous; fig. 100 D, asynchronous tetanus). An accurate mechanical record is therefore of more value as a

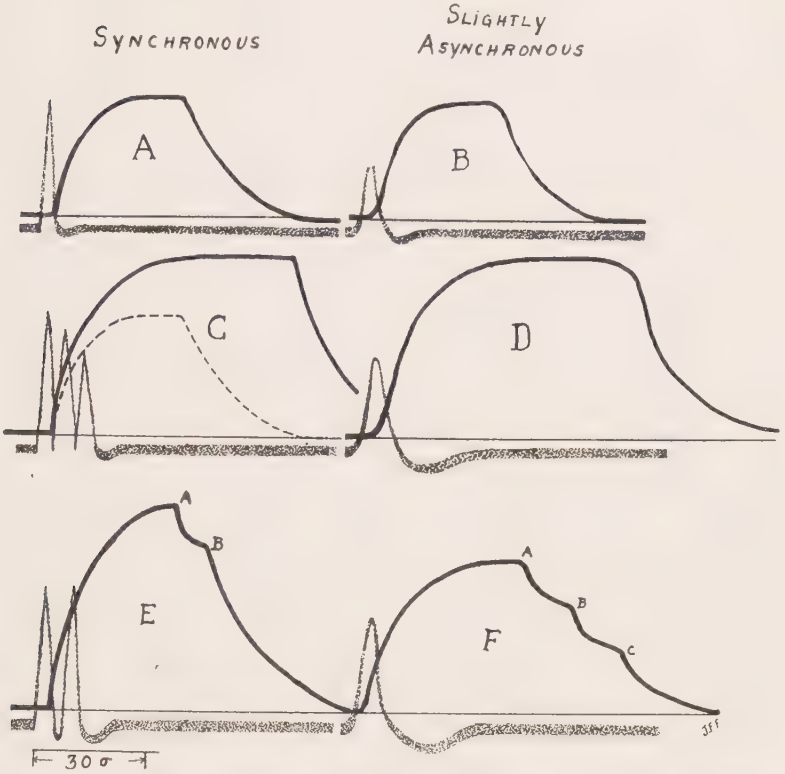

Fig. 100. A series of diagrams illustrating the various possibilities of summation of fibre responses in simple reflexes. The diagrams will convey to the reader in concise form the nature of the information provided by accurate mechanical and electrical records when obtained simultaneously, and they will also serve to clarify the method of analysis and interpretation of records obtained with this technique.

A. A response produced by a single *synchronous* volley of nerve impulses. Note the convex ascent, precise "angle" and concave relaxation.

B. Single *asynchronous* volley. Note "spread out" electrical response, and in the mechanical record the initial concavity of ascent and initial convexity of relaxation.

C. A tetanus produced by three *synchronous* volleys of impulses. Note the greatly increased duration over that of a single response.

D. A similar tetanus produced by *asynchronous* volleys. Note the modifications and that the electrical response does *not* reveal the tetanic character of the response. This type of response is typical of the knee-jerk.

E. Two groups of fibres in the same muscle responding at a brief interval after each other (9σ), each group responding synchronously. "A" and "B" indicate the successive "angles."

F. Three groups of fibres commence activity with approximate simultaneity, but the first group is stimulated twice, the second 3 times, the third 4 times, with the result that three "angles," A, B, and C are evident on the curve of relaxation.

criterion of repetitive firing in reflex responses than is the electrical response, which is often completely smothered as a result of the impulses of the volley (or a series of volleys) being slightly out of phase. It has been emphasized (*365*) that on account of this absence of string movement following a given reflex reponse, such as the flexor reflex, or the knee-jerk, does not necessarily indicate absence of repetitive after-discharge. *The presence of after-discharge can only be determined with certainty by an accurate mechanical record.*

4. Number of volleys. One can, moreover, estimate roughly from the duration of mechanical responses of short tetani the number of volleys composing the tetani (fig. 100 D). Thus it was found that, as a rule, spinal knee-jerks (*48*) fall into several groups of characteristic duration. In one experiment three groups were noted of average duration of 80, 105, and 130σ. These correspond with motor tetani of 3, 4 and 5 volleys respectively when the volleys are separated by intervals of 6 to 10σ. It may be inferred from this that the three groups of knee-jerks in question were *tetani* produced by 3, 4 and 5 volleys of nerve impulses respectively (Chapter XI).

5. Rate of discharge. It is sometimes possible to infer the rate of discharge from the combined mechanical and electrical records, for though, owing to asynchronism, the galvanometer string does not show the rate directly, it often shows how long the volleys continue (duration of string vibration following first response). Knowing the number of volleys from the duration of the mechanical record, it is therefore possible to calculate the rate. Such calculations, however, are never more than an approximation, since the "Dusser de Barenne-Buytendijk" vibration may be due in part at least to the polyphasic character of electrical responses observed by Adrian (*13*), when the galvanometer "leads" are not taken from the same fibres in the muscle (see Chapter I above).

A more accurate method of determining the rate of discharge has been found in an analysis of the time relations of inhibition of the knee-jerk. When an inhibitory stimulus falls at a brief interval (3 to $\pm$20σ) *after* the tap stimulus for a knee-jerk the duration of the jerk is diminished owing to inhibition of the terminal portion of the repetitive after-discharge. From other data it is known that an inhibitory stimulus affects discharging spinal motoneurones within 2 to 3σ after the moment of application to an afferent nerve trunk, and this is but little longer than the conduction time to the spinal cord (approximately 1σ). Now the least interval after the tap at which an inhibitory stimulus will *not* diminish the duration of the jerk provides an accurate measure of the duration of volley "firing." By this method accurate determinations of the rate of discharge are being made which will be described in the following chapter (Fig. 108B).

6. Irregularities in the curve of relaxation (*after-discharge*). From the shape of the curve of relaxation, it is often possible to detect whether all the motoneurones involved in a reflex response in which there is repetitive "firing," discharge the same number of times. In knee-jerks, for instance, one sometimes observes (*48*) a first somewhat smothered "angle" followed by a second "angle" (and sometimes a third), during the course of relaxation (fig. 100 E). This has been taken as indicating that a certain large portion of neuro-muscular units have responded, *e.g.*, 3 times, while the secondary undulations ("angles") on the curve of relaxation, give evidence of other groups of fibres which have responded 4 or 5 times, or more. The electrical response usually provides no indication whatsoever of these variations, and it may be repeated, their existence can only be inferred with safety from scrupulously accurate mechanical records. It is highly probable that the irregularly shaped curves of subsidence of many reflex responses (see below, fig. 112) are caused by this variety of after-discharge, *i.e.*, a large number of neuro-muscular groups each ("after"-) discharging repetitively a different number of times (*931*, *932*, Sherrington). But as we shall see other modifying influences such as the stretch reflex operate during relaxation and in this way modify the course of "true" repetitive after-discharge.

That these principles of interpretation of mechanical records are both necessary and adequate is evident from the fact that most of the variations described for reflex responses have been produced experimentally in response to motor nerve stimulation. Asynchronous single volleys of motor nerve impulses have not as yet been produced experimentally since every artificial method known at present of stimulating a motor nerve inevitably sets up a large number of impulses at the same moment of time. The characteristics, however, of the mechanical record and the electrical record have provided *indirect* evidence, which would appear overwhelming, that reflex responses, even when there is apparently no repetitive after-discharge, are invariably produced by impulses which are slightly out of phase with each other. Short tetani, on the other hand, of 2 and 3 volleys of impulses, or more, have been thoroughly investigated in motor nerve responses, and, as we have seen, the duration of those tetani, other things being equal, divide them into well-recognizable groups according as they are produced by 2, 3, 4 or more volleys of impulses.

When the electrical response is double and the interval between the two deflections very brief, (*e.g.*, 6σ), the reflex may be produced by a tetanus of two impulses ("wave" summation, see Chapter IV), or, as Forbes and Gregg have emphasized, "it may be readily explained as a double grouping

of the reflex times in the many individual arcs" (*320*, p. 175). In other words, two volleys may occur, but in different neuro-muscular groups, each unit responding but once (asynchronous multifibre summation). The mechanical response gives decisive and clear-cut evidence as to which of these two explanations is adequate in any given case (cf. fig. 100 F. with fig. 100 C). Thus, one finds experimentally that if the two roots, A and B, supplying the gastrocnemius muscle are stimulated one after another, by single shocks, the stimulus to B occurring 6σ after the stimulus to A, two electrical responses will occur in the muscle as a whole, but the "angle" of the mechanical response will be smothered owing to the fact that the two groups of fibres controlled by roots A and B do not commence and do not cease to contract at the same time; whereas, if the two roots are stimulated twice *simultaneously* at an interval of 6σ, two electrical responses will similarly occur, but the "angle" of the mechanical response will be as sharp as in a single twitch. Such motor nerve responses have already been described and analyzed in a previous chapter in the section on multifibre summation (see fig. 43). In the same way, other variations involving volleys of 2, 3, 4 or 5 impulses in various fibre groups at different time intervals have been analyzed experimentally by stimulation of the lumbar roots. In this way the method of analysis and interpretation of reflex responses have been amply justified and controlled by experimental procedure.

To summarize: It is possible to determine from the duration and configuration of an accurate mechanical record of a reflex response: (1) whether the response is produced by a single volley of impulses; (2) whether, if so produced, the volley of impulses reach the muscle fibres synchronously; (3) whether a reflex is a tetanus, and if a tetanus, (4) the approximate number of volleys in the tetanus and (5) the rate of their discharge; and (6) in after-discharge, whether all the elements discharge the same number of times.

CHAPTER XI

An Analysis of Elementary Reflexes: The Knee-Jerk and the Flexor Reflex

Accurate mechanical and electrical records of reflex responses, especially when the two are taken simultaneously, have thrown much light upon the nature of the central nervous processes by which these reflexes are evoked. In the previous chapters the behaviour of the peripheral muscular apparatus under various conditions of motor nerve stimulation has been studied in detail, and we propose now to use this knowledge for investigating the nature of central nervous processes. The recording muscle, in other words, is to be used as an *index* of the integrative processes occurring in the spinal cord and higher centres of the nervous system. We will first consider in some detail certain of the more simple reflex phenomena, namely, the knee-jerk and the flexor reflex.

THE KNEE-JERK

The knee-jerk has been studied in the past from many different points of view. Its clinical behaviour has proved a useful index of various diseases of the central nervous system, though uncertainty still exists concerning the significance of some of its abnormal variations. The nature of the knee-jerk has also for many years been a subject of controversy in physiological circles. Early investigators regarded the muscular response evoked by a tap on the patellar tendon as an "idiomuscular" contraction caused by sudden stretch of the muscle fibres. This view was urged on account of the extreme brevity of the reaction. It was stoutly maintained by Waller (*1014*) and others, and even at present one finds adherents to this early view (*582, 336*).[1] Other investigators, notably Bramwell (*145*), Bowditch and

[1] Frank's view as to the idiomuscular nature of the knee-jerk and other attendant phenomena may be illustrated by the following quotation from his work. "Das Sehenphänomen ist also eine idiomuskuläre Einzelzuckung, ausgelöst vom Sarkoplasma her und gebunden an den tonischen Zustand des Sarkoplasmas, welcher durch parasympathisch-motorische Dauerimpulse längs efferenter Bahnen der hinterin Wurzeln unterhalten und gesteigert wird" (*336*, p. 163). Other references to his own previous work and to the work of others who hold this view are to be found in the paper from which this quotation is taken (see also Chapter XVI of this work).

Warren (*141*), Lombard (*653*), and Sternberg (*970*), came on clinical grounds to regard the knee-jerk as a reflex phenomenon, for its absence was found to be definitely associated with certain lesions of the central nervous system. The view of the clinicians was strongly supported in 1893 by Sherrington's discovery that the knee-jerk could be inhibited centrally like other spinal reflexes (*875*). Waller and those who supported the idiomuscular view of the knee-jerk, replied to this observation that Sherrington had not inhibited the knee-jerk directly, but had inhibited that mysterious quality, the "tonus" of the muscle, without which the knee-jerk was incapable of being evoked. Though the majority of investigators probably did not

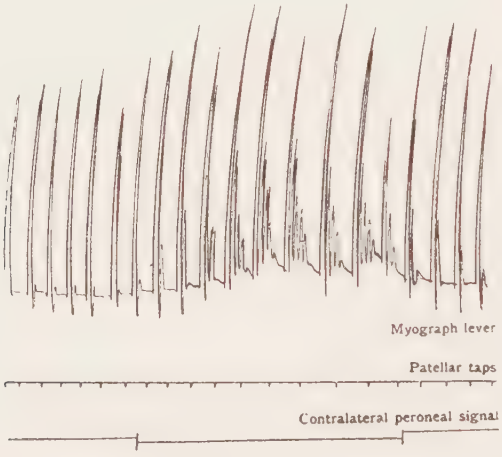

FIG. 101. Tracing a series of knee-jerk reflexes from a *spinal* preparation, showing the effect of contralateral peroneal stimulation upon the amplitude of the jerks. Note also that the "tonus" of the muscle becomes increased at the same time, *i.e.*, a crossed extensor reflex has occurred. (From Viets, *Brain*, vol. 43, p. 278, 1920.)

concede much importance to this objection, one still finds it in certain textbooks.

The knee-jerk, by many investigators, is believed to be a measure of the degree of tonus existing in the muscle. Under most circumstances this is undoubtedly true. In flaccid paralysis (*e.g.*, caused by lesions of the anterior horn cells) tonus is absent, and so is the knee-jerk. On the other hand, the knee-jerk usually increases in briskness, as many clinicians have pointed out, with increasing spasticity (*e.g.*, clinical decerebrate rigidity, *1023*). In clinical material one finds that the briskness of the knee-jerk rises with the extent of interference with the upper motor neurones, or in

other words with the extent of "release" from inhibitory control. But one is not wholly justified in believing that the knee-jerk is always an index of tonus, for ample jerks are to be obtained in spinal preparations in which tonus is largely absent. The case for the dependence of the knee-jerk upon the existence of tonus has been carefully investigated by Viets (*1002*). He finds that when the tonus is diminished by mild degrees of inhibition the knee-jerks are correspondingly diminished; or if the tonus of a muscle is augmented, *even in a spinal preparation*, by contralateral stimulation, the knee-jerks, within certain limits, are also augmented (see fig. 101). Viets's results have been well substantiated on other grounds by Paul Hoffmann (*493*), whose important monograph on tendon phenomena was published in 1922. His work will be discussed more extensively when dealing with the problem of voluntary contraction.

We shall see in a later chapter that the apparent absence of tonus in "spinal" animals is associated with an increased susceptibility of the anterior horn cells to inhibition, a condition which affects the tonic responses without apparently affecting the knee-jerk itself.

The chief objection to the reflex nature of the knee-jerk raised by the idiomuscular adherents: namely, the extreme brevity of its latency, was effectually removed almost simultaneously (1910) by three independent investigators, Jolly (*523*), Snyder (*952*) and Dodge (*237*), who measured the latency of the knee-jerk with accuracy, and though they found it even briefer than had hitherto been supposed, they nevertheless established,—in view of the extreme rapidity of conduction in mammalian nerve fibres demonstrated by Piper (*774*) (approximately 120 metres per second),—that the short latency could not be legitimately urged against the knee-jerk being a reflex. Jolly, for instance, found that the interval between the tap on the tendon and the beginning of the muscle action current may be as brief as 6σ; in the majority of his experiments it was somewhat greater than this, and in many it was as large as 11 or 12σ. Jolly subtracted the time required by the nerve impulses to traverse the distance to the cord and back again to the muscle, and from this obtained what he called the "reduced reflex time,"—the time, in other words, consumed by the nerve impulse in passing through the spinal cord. Jolly emphasized, in view of the brevity of the reduced reflex time (approximately 2σ), that the knee-jerk must be a purely spinal reflex. The afferent impulses, in other words, do not pass through the centres of the midbrain before returning again to the muscle. Jolly's investigations were substantially confirmed by Dodge and Snyder.

Mechanical records of the knee-jerk have been made in the past, but in most cases the method of recording was not of sufficient accuracy to admit

of detailed analysis of the shape of the response. Recently Ballif, Fulton and Liddell (*48*), using an optical isometric lever of the Sherrington pattern described in the appendix to this work, have obtained the mechanical and electrical responses on the same photographic plate. They compared the characteristics of the knee-jerk in spinal and decerebrate preparations with those of the motor nerve twitch of the same muscle (the quadriceps extensor). Certain characteristic differences between the decerebrate and spinal knee-jerks and motor twitches were observed, which may be described as follows.

The decerebrate knee-jerk and the motor twitch. The characteristics of the mechanical record of a motor twitch, described in Chapters II and III: namely, (1) the period of rigidity previous to shortening, (2) the abrupt and almost completely convex (upward) ascent, (3) the flat crest or plateau, (4) the terminal "angle," and (5) the concave descent, are all to be found in the decerebrate knee-jerk, but in somewhat modified form. The period of rigidity is less precise and more difficult of accurate measurement, the ascent of the knee-jerk is possessed of a somewhat higher point of inflection from concavity to convexity, though the actual steepness of the ascent may be *greater* than that of a motor twitch, the plateau of the knee-jerk tends to be somewhat greater in duration than the twitch crest, the "angle" of the knee-jerk, though often very precise, is nevertheless more rounded than that of the twitch under comparable conditions, and, finally the curve of relaxation is characterized initially by a slight convexity or "nose." The duration of the decerebrate knee-jerk, measured from the electrical response to the "angle" was found always somewhat greater than that of a motor nerve twitch. In some cases it was greater by only 3 or 4 per cent. In six preparations decerebrate knee-jerks were obtained, which were 40 to 45σ in duration, while the duration of the motor twitch, taken subsequently under as nearly as possible the same conditions of temperature and initial tension, had durations ranging from 37 to 40σ. In other decerebrate preparations, however, the knee-jerk was sometimes 50 per cent (60σ), and in a few cases sometimes 100 per cent (80σ) greater than the corresponding motor twitch. The differences between the knee-jerk and motor twitch can be brought out by comparing figure 100 A with 100 B. From the discussion in the last chapter, it is evident that the less precise period of rigidity, the higher point of inflection, the longer plateau, the less precise "angle," the "nose," and finally, the increased total duration, taken together, indicate that in the decerebrate knee-jerk the participating muscle units do not all respond synchronously,—even in the case of jerks elicited by the briefest stimuli ($\pm 1\sigma$).

It may be pointed out that the motor twitch was less in duration than the knee-jerk contraction despite the progressive cooling which may have occurred as a result of exposure of the muscle.

It was found also that the duration of the knee-jerk varied to a certain extent with the nature of the tap. It was possible, with the recording apparatus used, to measure accurately the time required for the kinetic energy of the tap to be transferred to the tendon; that is to say, one could read directly from a record the duration of the tap stimulus. In the majority of the records, the time required for the kinetic energy of the tap to expend itself upon the tendon was as brief at 1 to 2σ. It was inferred, therefore, that probably only one volley of afferent impulses were set up by a tap of this brevity. This appears justifiable, moreover, in view of Adrian's (*13a*, *19*) recent analysis of the rate of response of a single "stretch-afferent" end-organ in a muscle. When, however, a "slower" tap was delivered, one often observed knee-jerks of greater duration and less precise mechanical characteristics (modified "angle," etc.). This was interpreted as indicating that the volley of motor impulses in the case of the "slow" knee-jerk reached the muscle less synchronously than in the case of a "quick" knee-jerk. This is probably due to *serial* stimulation of afferent endings in the muscle, caused by the more gradual nature of the tap, but it does not, however, rule out the possibility of repetitive *afferent* firing of the tendon organs, which may possibly occur with a slow tap.

The following contributing factors have been suggested as the cause of temporal dispersion in the knee-jerk. (1) The conduction-time of the wave of increased tension[2] up or down the muscle may be considered, but recent observations of Bethe and Happel (*97*) indicate in the case of the isolated sartorius of the frog that the conduction time of the tension wave may be of the order of 1σ per centimeter. If this value held for the quadriceps, and if one assumes that the afferent terminations are distributed equally throughout the entire muscle, the afferent volleys of impulses would be spread over 8σ; but as the muscle is initially stretched, it is likely that 8σ is a high estimate. (2) The slightly differing conduction rates in an apparently homogeneous volley of nerve impulses, which Erlanger and Gasser (*386*, *287*) have demonstrated by means of the cathode ray oscillograph, would tend to cause the volley of impulses to spread out slightly as they travelled up and down the nerve. (3) The duration of the tap itself is not less than 1 to 2σ, as contrasted with the brief duration of an inductorium stimulus. (4) Perhaps the most important cause of asynchronism is the variation in the latent time of central nerve cells and synapses. Forbes and Gregg (*320*) found with a single instantaneous induction stimulus, that the flexor reflex response was also produced by a somewhat asynchronous volley. It is evident therefore that the asynchronous volley of the knee-jerk is probably not due entirely to serial stimulation of the afferent endings. Forbes (*318*, p. 387) has suggested that the central asynchronism may be accounted for by the assumption that individual impulses may pass along very different and branching reflex paths; this would indeed seem the most likely explanation of the observed asynchronism in the knee-jerk of a decerebrate preparation and the flexor reflex, but, as we shall see presently, it does not provide an adequate explanation of after-discharge.

The spinal knee-jerk. The knee-jerk of a spinal animal, whether of a decapitate preparation or of a decerebrate preparation made "spinal" by

[2] It was found that the knee-jerk is approximately the same in its duration and shape whether elicited by a tap on the tendon or by a tap on the table which held the muscle.

transection of the cord in the thoracic region, is characterized by the same mechanical features as in the case of the decerebrate jerk, but there are certain constant and outstanding differences between the decerebrate and the spinal jerks, which are summarized in the following paragraphs. The reader will be assisted in following the description if he compares figures 102 and 103, which show series of decerebrate and spinal knee-jerks (see also below, figures 127 and 128).

1. The *latency* of the spinal knee-jerk, by which is meant the interval between the beginning of the tap and the commencement of the electrical

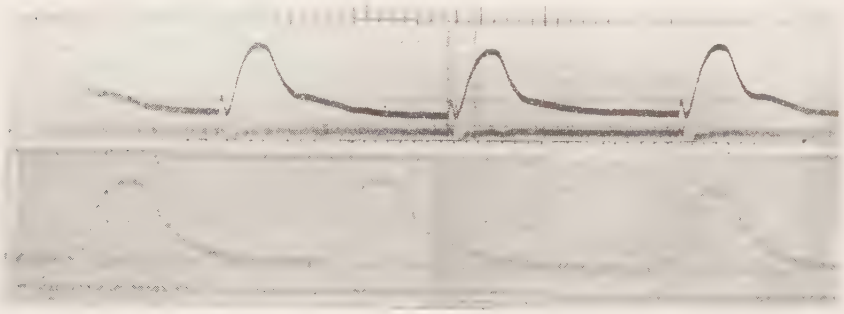

FIG. 102. A record of three successive knee-jerks of a decerebrate preparation. In each case the initial upstroke before the main reaction is caused by the tap on the tendon. For other conditions of the experiment, see below (fig. 127, Chapter XIII). The average duration of jerk in these figures is 60σ. Shortly after a "high" decerebration the jerks of most preparations are ordinarily only 40 to 45σ. Often they jump to a duration 60 to 65σ in the course of an experiment.

FIG. 103. The knee-jerks of the same preparation as in figure 102, a few minutes after having been made "spinal." The average duration of these jerks is now 100 to 105σ. Often spinal jerks become 120 and 130σ in duration, maintaining at the same time their sharp "angles."

response, tends in the majority of preparations to be greater in the spinal condition than in the decerebrate; thus, in the majority of our records the decerebrate knee-jerk has a latency lying between 5.5 and 7.5σ with an average of 6.8σ, while the spinal jerk had a latency between 7 and 10σ with an average of 8.5σ. The cause of this slight difference may be either central or peripheral in origin. In the case of the decerebrate jerk the tension of the muscle is presumably maintained by active contraction of a certain proportion of muscle fibre constituents (Chapter XVI), while in the "toneless" spinal muscle, the passive tension is maintained by *inactive* constituents. Under such circumstances it may be that more time is lost in setting up an effective stimulus of the muscle end-organs. On the other

hand, the condition of the central nerve cells of the spinal cord is demonstrably different in the spinal condition than in the decerebrate, and may therefore be possessed of slightly different latency, but one cannot decide definitely between these two possibilities. In several preparations no differences in the latency were found; consequently one need not attach great importance to difference usually found.

2. Of much greater importance, however, is the fact that the *duration* of the spinal knee-jerk is regularly 100 to 200 per cent greater than the duration of the decerebrate jerk. Despite this increased duration, the ascent is usually very abrupt, though as a rule not quite as abrupt[3] as in a twitch; moreover, the plateau is flat and the "angle" is sharp. The different durations of the two types of knee-jerk is the most important and the

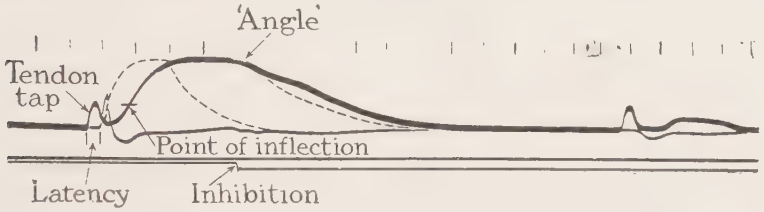

FIG. 104. Knee-jerk of spinal preparation taken on "fast" plate to show the interval between the tap and the action current—in this case 8.4σ. The point of inflection on the mechanical ascent is shown, as well as the "angle." The duration of the response is approximately 82σ, as contrasted with a motor twitch shown as a dotted line of 38σ. The rate of rise of the twitch is somewhat too rapid. An inhibitory stimulus is applied at the moment indicated. The ipsilateral twitch resulting from this has modified the relaxation; the unmodified course of the relaxation is shown by a dotted line. The second response to a tap on the tendon is very small, owing to the long-lasting effect of the single inhibitory stimulus. The duration of this second response is approximately 40σ. Time intervals, 0.02 second. (Ballif, Fulton, and Liddell, *48*).

most constant of their distinguishing features. In figure 104 a spinal knee-jerk has been reproduced and a dotted line on the record indicates the duration of a motor twitch of the same muscle.

3. *Electrically*, the difference between the decerebrate and spinal knee-jerks are very slight (figs. 102, 103). In general it may be said that the electrical response of the spinal jerk is somewhat more spread out and, when comparable leads are taken from the same muscle in the two conditions, the second deflection of the diphasic excursion of the galvanometer string is more prolonged in the spinal response and is sometimes possessed

[3] Though the commencement is less abrupt, the ascent may be and usually is, *steeper* in spinal jerks than in decerebrate jerks or motor twitches.

of slight rhythmic vibrations of the de Barenne-Buytendijk type; moreover, for a given degree of tension development, the electrical response is often larger in the spinal jerk than in the decerebrate, but aside from these slight and often inconstant differences, the action current of the spinal knee-jerk is indistinguishable from that of the decerebrate knee-jerk. There is, in other words, no clear-cut electrical evidence of repetitive discharge of the neuro-muscular units.

4. Another important difference between the decerebrate and spinal jerk is in the shape of the *curve of relaxation*. In the spinal jerk it is usually less steep, and in the majority of records smooth. In the decerebrate jerk, on the other hand, the initial portion of the curve of relaxation is steeper than in the spinal jerk, but at approximately half-relaxation a "hump" is to be seen (fig. 105; also 102), which was first described by Sherrington (*927*, p. 211) who regarded it as a "shortening reaction." This hump is to be

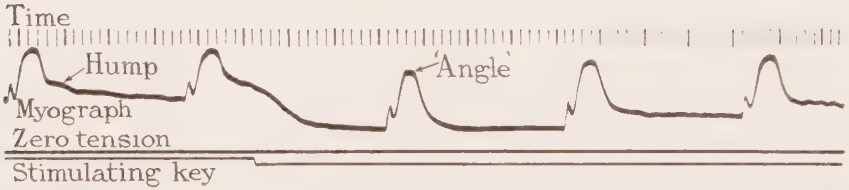

FIG. 105. A series of knee-jerks of a decerebrate preparation. Note relaxation of tonus following single inhibitory break-shock. Electrical responses not recorded. Note that after inhibition the "angles" are sharper and the duration of the responses somewhat more brief. The durations in this record lie between 40 and 50σ. Time, 0.02 second. (Ballif, Fulton, and Liddell, *48*.)

observed only in tonic muscles, and, as we shall see, it may be inhibited centrally in the same way that other postural reflexes can be inhibited. Ballif, Fulton and Liddell (*48*) have regarded it as a myotatic appendage of the decerebrate jerk being probably elicited by the sudden stretch resulting from the abrupt cessation of contraction of the jerk. They referred to the period preceding the "angle" of the decerebrate jerk as the *kinetic* phase of this reflex. The cessation of this kinetic phase causes the myograph lever to deliver a sudden stretch to the tendon, in this way serving as an adequate stimulus for a reflex contraction (the hump). We will see in a later chapter how the "shortening reaction" similarly appends itself to the curve of relaxation of quadriceps from other reflexes (*e.g.*, the crossed extensor). When the degree of freedom for shortening is greater than in these "isometric" records, a tonic muscle will produce an indefinite number of these myotatic appendages; in other words, it passes into a state of

clonus, or rhythmic contraction (see below). Under other circumstances the myotatic appendage may be continuous instead of rhythmic, and under such circumstances it is indistinguishable from the shortening reaction. This is mentioned here to bring out the probable relation between the myotatic appendage of the decerebrate knee-jerk and clonic responses, which are so well known clinically.

Undulations, or secondary "angles," which are sometimes observed in spinal knee-jerks (see fig. 106) are not to be confused with the hump of the decerebrate jerk. These undulations, when they occur in the spinal jerk are irregularly placed in the course of relaxation and they are always preceded by a precise "angle."

It is evident from what has just been said, that two varieties of after-discharge of the knee-jerk are to be distinguished, viz., repetitive firing, or true after-discharge, and the variety which has been termed the myotatic appendage which is undoubtedly a secondary stimulation resulting from the stretch reflex.

5. A less important difference between the spinal and the decerebrate jerk is that generally the interval between the electrical response, and the active contraction is greater in the spinal condition than in the decerebrate. This again is, in all probability, to be associated with the fact that in the tonic muscle the passive tension is maintained by active contraction of a small proportion of the fibre unit while in spinal condition this passive tension is maintained by inactive muscle constituents.

6. In the case of elicitation the decerebrate knee-jerk presents a marked contrast to the spinal. Other things being equal, the initial tension of the muscle must be from 100 to 300 per cent greater in the spinal condition for the knee-jerk to be elicited by a comparable tap on the tendon. Under the same initial tension (*e.g.*, 200 grams) of the muscle the tap in order to be effective in the spinal preparation must be several times more intense than suffices in the decerebrate (as judged by the initial upstroke of the myograph—cf. figs. 102 and 103). In this connection we have found the threshold for the elicitation of the jerk much higher in a spinal preparation in which the spinal transection was made before decerebrating, than in a preparation which had been allowed fully to recover from the anaesthetic (and the decerebration) and which was made spinal several hours later (with anaesthetic). No adequate explanation was found for this observation.

7. Dr. G. P. McCouch has very kindly drawn my attention to another difference between spinal and decerebrate jerks observable in our records, namely, that the "angles" of the decerebrate jerks are less precise than those

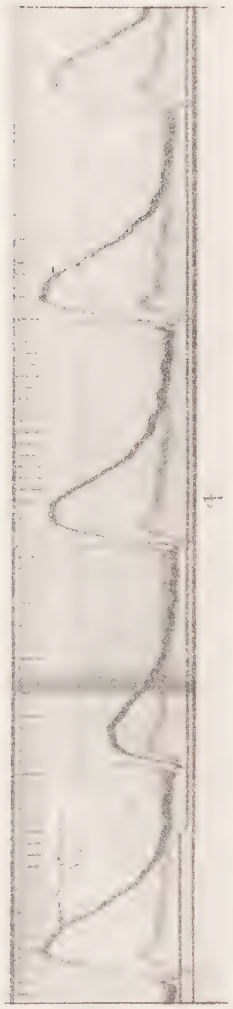

FIG. 106 A series of spinal knee-jerks ("aseptic" spinal preparation) in which several mechanical responses (1 and 4) do not show a clear "angle," but exhibit a series of undulations on the curve of relaxation. This can be interpreted as evidence of asynchronous cessation of contraction in the individual responses, due presumably to an unequal number of repetitive "discharges" reaching groups of individual muscle fibres (see above, fig. 100 E). (Ballif, Fulton, and Liddell, *48*).

of the spinal, suggesting, as Dr. McCouch pointed out, that the decerebrate responses, grafted as they are upon a background of tonic rigidity, are less synchronously produced than spinal jerks, which lack this background. Examination of other records of "acute" preparations has revealed this same distinguishing characteristic, and it is therefore clearly of importance. When the tonus is inhibited as in figure 105, the "angle" of the succeeding jerk becomes sharper.

SIGNIFICANCE OF DIFFERENCES BETWEEN THE DECEREBRATE AND THE SPINAL KNEE-JERKS (*48*)

The increased duration of the spinal knee-jerk above that of the decerebrate might be accounted for in one of several ways. It may be urged that though the sensory impulses arrive at the spinal cord almost synchronously, the larger number of branching "delay paths," as Forbes (*318*) has termed them, might cause the efferent volleys of impulses to emerge separated out into a prolonged but single volley, in which the first impulse reached the muscle 50 to 100σ before the last (temporal dispersion), in this way producing a prolonged response such as one observes in spinal knee-jerks. This explanation is definitely ruled out of court by the abrupt ascent on the one hand and the sharp terminal "angle" on the other. The existence of this latter discontinuity provides evidence that a large proportion of muscle units have ceased to contract at the same time. This would, of course, be impossible if the individual elements responded (singly) over a period of 50 to 100σ.

A second possible explanation is that red muscle fibres, which have a more prolonged contraction period (Chapter IV), respond in case of spinal jerk, and that pale fibres respond in the case of the decerebrate jerk. Apart from the inherent improbability of this explanation, it is made unlikely by the fact that the "angle" observed in the spinal jerk may be almost as precise as a white fibred twitch, while the "angles" of red muscle fibres are always more rounded. Moreover, the electrical response of red muscles is four times longer than that of white muscle of the cat, and no such prolongation of the spinal electrical response has been observed. However, this may be, soleus, which is a red muscle, yields in a decerebrate cat an ample tendon jerk, more readily in fact than does gastrocnemius (Denny-Brown).

A more likely explanation is that *the spinal jerk is in reality produced by a short tetanus,* in which all of the responding neuromuscular units discharge repetitively. Against this explanation is, of course, the apparent absence of any electrical manifestations of such a repetition, but it may be

emphasized at once that if the repetitive discharge recurred at brief intervals of 5 to 10σ, and each unit failed to discharge at precisely the same instant any evidence of repetition would be smothered and incapable of

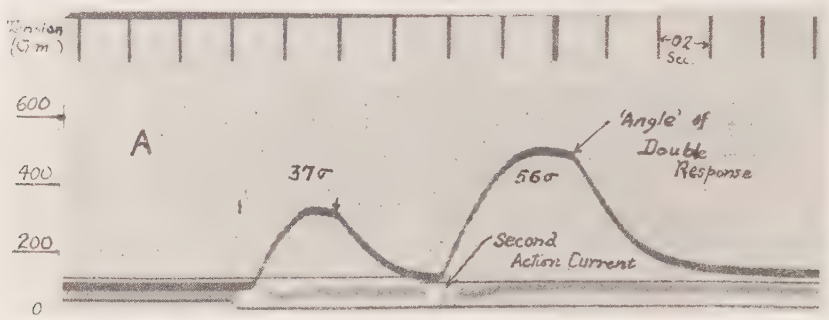

FIG. 107. Single response (duration 40σ) followed by double response (duration 65σ), the second stimulus being a supramaximal "make" of a coreless coil. The interval between the two action currents of the fused response is approximately 5σ. Frequency of myograph 500 per second. T = 24°. Time above = 0.02 second. (Ballif, Fulton, and Liddell, *48*.)

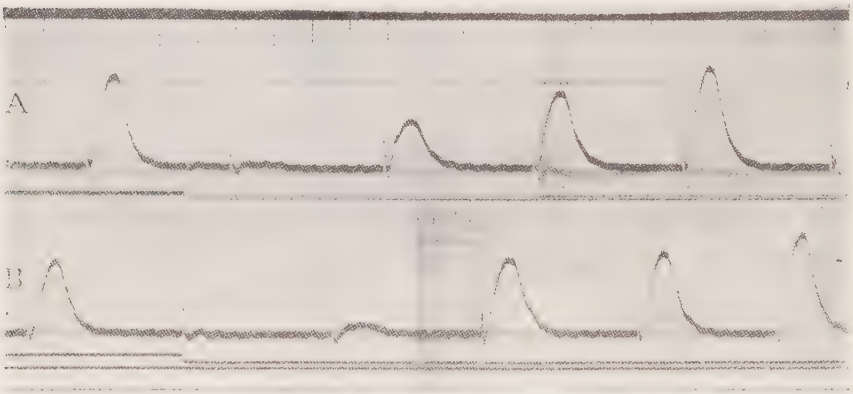

FIG. 108. Knee-jerks (spinal) showing gradual recovery from an inhibitory stimulus. In B the tap and the inhibitory stimulus are nearly simultaneous, the inhibition occurring 1 to 1.5σ *after* the beginning of the tap, but the inhibition is nevertheless effective.

being recorded by the galvanometer string. In figure 107 a double motor nerve response is shown in which the second action current occurred 5.5σ after the first, *i.e.*, when the galvanometer string was returning to its base

line at a high velocity. There is then an algebraical summation of the downward movement with the attempted upward movement, which has resulted merely in the short hesitation of movement of the string. Now this second volley shown in the figure represents a simultaneous response of a large number of fibres. Had this second volley been slightly spread out, even by as little as 0.4σ there would have been no easily recognizable evidence of its having occurred, apart from a very slight prolongation of the downstroke of the deflection. Moreover, in a few records of spinal jerks, as has been mentioned, a slight Dusser de Barenne-Buytendijk vibration was observed during the diphasic swing, which possibly indicated in those records repetitive firing.[4] *Mechanically* the evidence for repetitive firing is much more clear-cut. If, as shown in figure 107, one stimulates a motor nerve twice at an interval of 5.5σ the duration of the resulting fused response is roughly 50 per cent greater than a single response. If one delivers a tetanus of three similarly timed impulses the duration of the mechanical response so produced is about 80 per cent greater than a single response, of four volleys, 105 per cent, etc. Now these are precisely the groups into which the spinal knee-jerk durations fall. Thus one observes among large numbers of spinal knee-jerks groups approximately 50 per cent longer than a twitch, more frequently they are 80 per cent longer, usually they are about 105 per cent longer, though often they are considerably longer than this. Further observations on this point are being made. The fact that the ascent of spinal knee-jerks, though ordinarily of more gradual onset, are nevertheless usually *of steeper incline* than motor twitches of the same size is difficult to explain on any other grounds than that of repetitive firing.

INHIBITION OF THE KNEE-JERK

The inference that the knee-jerk of a spinal animal is in reality a short tetanus has been strengthened by a study of the behaviour of the knee-jerk during and just after inhibition. A more detailed analysis of the inhibition of the knee-jerk will be given in a later chapter devoted to the features of the central inhibitory process. For the present argument, it may be pointed out that both decerebrate and spinal knee-jerks are capable of being inhibited by single break induction shocks when appropriately timed, but the decerebrate jerk is much less susceptible to an inhibitory stimulus than is the spinal jerk. If, in the spinal animal, a maximal inhibitory stimulus (break shock) is delivered to the ipsilateral hamstring nerve

[4] It is not well to place too much faith upon this evidence of repetitive firing, for this type of vibration might be caused by the polyphasic character of the single response.

during a series of knee-jerks recurring at approximately 3 per second, as many as 5 successive jerks may be completely inhibited following such a stimulus. Then follows a period of gradual recovery. The first knee-jerks to appear after the period of complete inhibition are of sub-normal magnitude and if the size of the jerks is plotted against time during the period of recovery, it is found that a smooth recovery curve results (fig. 125). Now it is a point of considerable significance that *the first knee-jerk to recover after such an inhibitory stimulus is of exactly the same duration as a motor nerve twitch, i.e., 40σ.* At 50 per cent recovery the jerks are usually between 40 to 60 per cent greater than a twitch (see fig. 128). At full recovery they may be twice or thrice the duration of a twitch. There would appear but one interpretation of this observation, namely, that the first spinal motoneurones to recover from the inhibitory stimulus are able to respond but once. When half of them have recovered the majority of the participating motoneurones respond twice. When recovery is complete the repetitive discharge is more extensive and probably consists of between 4 and 8 volleys of impulses.

In the absence of discrete electrical responses any determination of the number and rate of repetition of the volleys in a spinal knee-jerk must necessarily be an approximation. The rate and number were, however, tentatively inferred from two lines of evidence. (1) It was mentioned above that the diphasic portion of the excursion of a spinal knee-jerk sometimes shows minute vibrations, and as this is the only electrical evidence of repetitive firing, the interval during which the vibration occurs will give some indication as to how long actually the volley-fire persists. In the majority of records this interval is 30 to 40σ in duration (see fig. 103). (2) Mechanical records of short tetani applied to motor nerves have shown that a tetanus of 4 to 8 volleys, when the interval between the volleys lies between 4 and 10σ, gives rise to a mechanical response which is of the same order of duration as that of the spinal knee-jerk, *i.e.*, 90 to 140σ. It was inferred from this somewhat indirect evidence that the knee-jerk of a spinal preparation is produced by a short tetanus consisting of from 4 to 8 volleys of motor nerve impulses recurring at 100 to 200 per second. The complete asynchronism of these volleys suggests strongly that the motor nerve impulses do not follow in each motoneurone at the same rate, —a conclusion which is well in keeping in recent observations of Forbes and Olmsted (*323*).

After the publication of the above observations on the knee-jerk (*48*), it was found that the conclusions regarding the duration and *rate* of volley-fire were supported and amplified by a wholly different type of evidence which at the time of publication had not been considered. In a certain

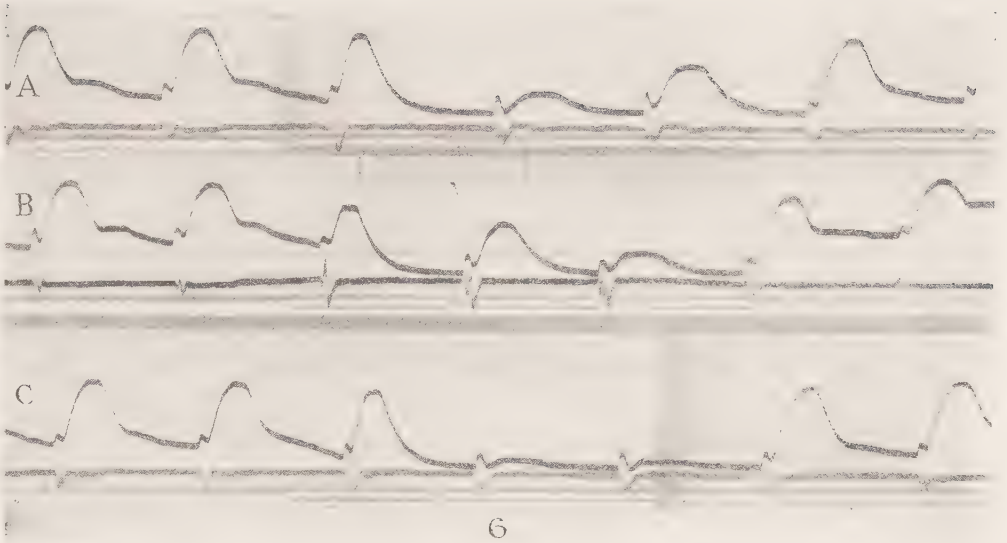

FIG. 109. Knee-jerks from a decerebrate preparation with marked extensor rigidity, showing inhibitory stimuli which were more effective on a second knee-jerk than on the first immediately following the stimulus. In C the duration of the first knee-jerk after inhibition is 40σ as contrasted with the normal jerk of 63σ. Also, the action current is much larger in this response than in the normal response preceding it, suggesting absence of repetitive firing as well as more perfect synchronization. Though a decerebrate preparation, the recovery of the second and third knee-jerks in A is gradual and distinctly spinal in character, suggesting that the mid-brain centres have been inhibited, making the preparation for a brief interval functionally spinal. The shadow of the galvanometer string has been "touched" to make it clearer. (Ballif, Fulton, and Liddell, *48*.)

number of Ballif, Fulton and Liddell's records the inhibitory stimulus fell soon enough *after* the tap to *diminish the duration of the* (spinal) *knee-jerk without inhibiting it.* Quite apart from the fact that this is perhaps the best evidence we have in favour of the tetanic nature of the spinal knee-jerk, it also shows that when the volley-fire is once in progress it may be cut short by an inhibitory stimulus. Now the least interval at which an inhibitory stimulus will *not* cut short the assumed volley-fire (as indicated by the duration of the jerk) was found to be approximately 30σ. A simple calculation shows that if 5 to 7 volleys recur within 30σ the natural frequency of discharge must lie between 175 and 250 per second; but *not higher than 250 per second* (cf. *323, 17*). For example, if 6 volleys recur during 30σ, the interval between them is 5σ, and hence the rate of discharge 200 per second. Further observations on this point are in progress.

When studying the inhibition of the knee-jerk our attention was frequently drawn to irregularities in the size of the action currents of jerks which mechanically were of the same or approximately the same size (*i.e.*, tension). We noted this most frequently in decerebrate knee-jerks following inhibition. It will be seen in figure 109 that the decerebrate knee-jerk quickly recovers from an inhibitory stimulus; that is it recovers its original size, but the *shape* of the jerk following inhibition is frequently modified. It was noted, for instance, that in a series of jerks in which 200 grams tension were regularly developed the action current is only 1 to 2 mm. in size. The ascent of these records had a relatively high point of inflection and the mechanical angle was not precise. The first knee-jerk, which followed at 0.10 second *after* the inhibitory stimulus, had an abrupt ascent and sharp angle and developed approximately the same mechanical tension as those preceding inhibition (fig. 109). The electrical response of this jerk was 10 mm. in amplitude, but the *duration* measured to the "angle," was 50 per cent less than the duration of its predecessors. We have, in this observation, a clear example of two jerks of the same mechanical tension but differing in mechanical characteristics of shape. The action current of one appears to be smothered; the current of the other is normal, that is to say, twitch-like in character. The mechanical features of the jerks before inhibition exhibit,—according to criteria for synchronization outlined in Chapter X,—all characteristics of an asynchronous response. There seems therefore to be but one interpretation of this result, namely, that the knee-jerk following inhibition was produced more synchronously, and was composed of but one single impulse volley, as judged by its duration. This observation warns against unrestricted acceptance of electrical evidence of muscular activity when, as in the majority of reflex responses, the individual

nerve impulses passing down the motor nerve appear to be more or less completely out of phase with each other (cf. Dusser de Barenne and Brevée, *259*).

THE FLEXOR REFLEX

For the study of repetitive discharge in reflex processes, the flexor reflex has certain advantages over the knee-jerk, for it is possible to set up this reflex by a known single volley of afferent nerve impulses. In the knee-jerk there is always the possibility that the afferent end-organs in the muscle respond repetitively, even though the tap stimulus is of extreme brevity.

As is well known, the flexor reflex is elicited by stimulating any ipsilateral sensory nerve in the hind limb. A large group of muscles take part in the response (Chapter XVIII) but the responses of semitendinosus and tibialis anticus have been most thoroughly studied. The reflex may be elicited both in spinal and in decerebrate preparations. The electrical responses of this reflex were made the subject of an important investigation by Forbes and Gregg (*320*) in 1915, while the mechanical aspects of the reflex have been studied most thoroughly by Sherrington and his collaborators (*246*, *637*, *845*, *931*, *932*, *943*). Combined electrical and mechanical records have been made in the course of the present investigation and further observations on the subject, as yet unpublished, have been made by Denny-Brown and Liddell (*233*). We shall consider first the electrical responses in this reflex in order to preserve the historical sequence of our knowledge of the subject.

Electrical responses. Forbes and Gregg recorded the electrical responses of the motor nerve to *tibialis anticus*, as well as the muscle action currents, when the flexor reflex was elicited by single induction shocks. They used decerebrate preparations throughout. Their attention was first directed to a study of latency of this response and they found that an interval between the moment of stimulation and the beginning of the action current ranged between 7.7 and 12.8σ. By subtracting the conduction time in the motor nerve they estimated that the "reduced reflex time" normally lies between 3 and 5σ. This was in keeping with the previous estimate of Jolly (*523*) who found in spinal and decerebrate preparations that the reduced reflex time was approximately 4σ. This is the interval, in other words, which is consumed in passing through the spinal cord, and is approximately double that of the "reduced reflex time" of the knee-jerk ($\pm 2\sigma$) (see below, p. 320).

The responses of the nerve were of course very much smaller than the muscular responses, but in both nerve and muscle Forbes and Gregg made

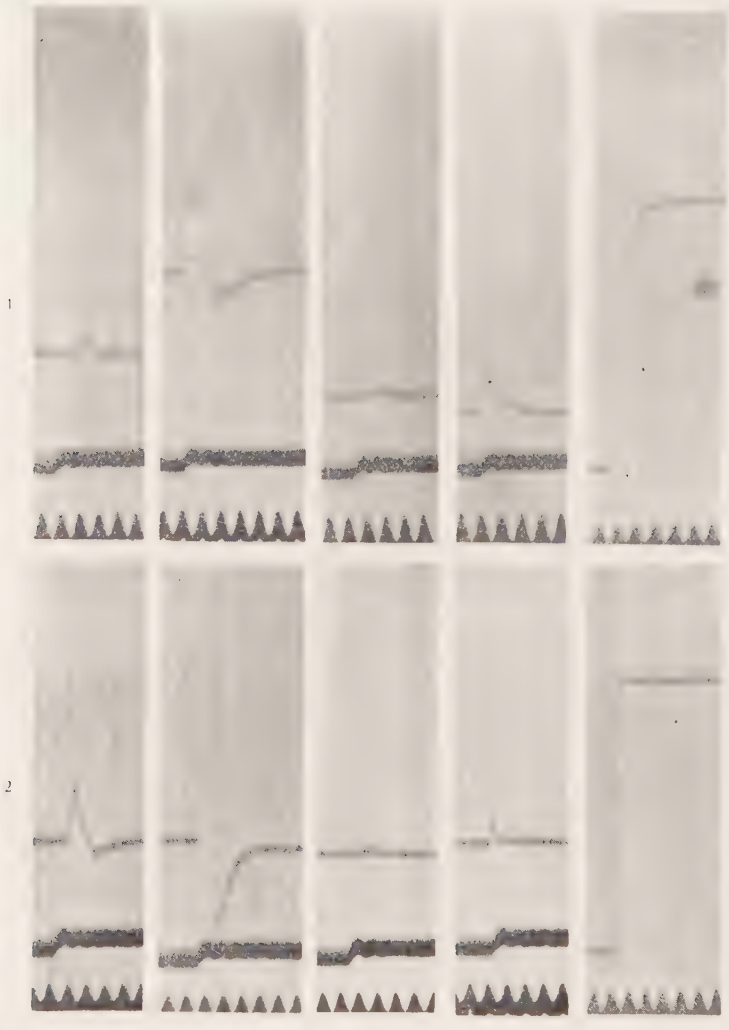

FIG. 110. Electrical responses of the flexor reflex (*tibialis anticus*) of a decerebrate preparation contrasted with the direct motor nerve response.

A. Reflex response of muscle.

B. Action current of muscle in response to stimulus applied to motor nerve.

C. Reflex *nerve* response (nerve to tibialis).

D. Response of nerve to direct stimulation.

E. Calibration curve of galvanometer (slack in 1) (Forbes and Gregg, *Amer. Journ. Physiol.*, vol. 37, p. 159, 1915.)

this important observation: that the action current of the reflex response rose more slowly to a maximum both in nerve and muscle than did the action current of the direct response (fig. 110); it was also much smaller in amplitude than the direct response and subsided less rapidly. They inferred from this that the volley of impulses of the reflex response was somewhat spread out owing probably to differing reflex times in the various paths pursued by the impulses in the spinal cord. They observed further that the response was frequently dicrotic in character and sometimes clearly double (fig. 111). They insisted that the double nature of the action current did not necessarily indicate repetitive discharge of the central neurones, but that it may readily be accounted for by the assumption of a double grouping of reflex time in many individual arcs. Each individual

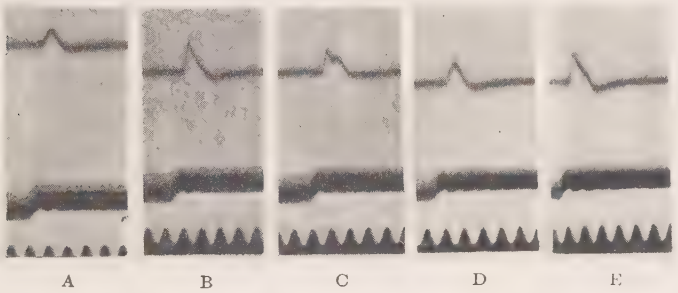

FIG. 111. Reflex electrical responses of *tibialis anticus* of decerebrate cat. B to E show the dicrotic character of the electrical responses often observed. (Forbes and Gregg, *Amer. Journ. Physiol.*, vol. 37, p. 162, 1915.)

element, according to this interpretation, responds only once, but one group of neurones has a greater latency than the other group, and hence the temporal dispersion. Further light upon these two alternatives is thrown by a study of the mechanical responses.

Mechanical responses. In a contribution by Sassa and Sherrington (*845*) on the "myogram of the flexor-reflex evoked by a single break shock," they have found: (1) that the *duration* of the contraction both in the decerebrate and in the spinal preparation was greater for the reflex response than for the twitch; (2) that the tension crest was reached relatively later after the onset of the contraction than in the motor nerve twitch, and the reflex crest-height frequently exceeded that of a maximal motor nerve twitch. They further observed that under successive increase of the

strength of stimulus the reflex contraction continues to increase through a far longer range of stimulus increments than in the case of the motor twitch; they found, (3) that the *steepness of the ascent* tended usually to be greater in the reflex responses especially when the crest-height of the reflex response was greater than that of the maximal twitch; and (4) that the contraction was more abrupt in the twitch response than in the reflex, indicating a higher point of inflection in the latter response. These distinguishing features were found to be present after the muscle in question (tibialis anticus) was deafferented by appropriate posterior root section (sixth, seventh,

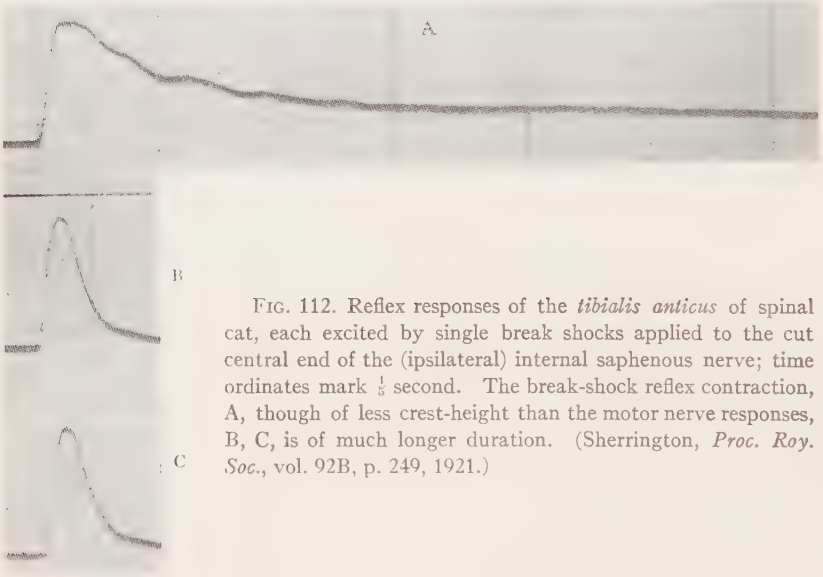

FIG. 112. Reflex responses of the *tibialis anticus* of spinal cat, each excited by single break shocks applied to the cut central end of the (ipsilateral) internal saphenous nerve; time ordinates mark $\frac{1}{5}$ second. The break-shock reflex contraction, A, though of less crest-height than the motor nerve responses, B, C, is of much longer duration. (Sherrington, *Proc. Roy. Soc.*, vol. 92B, p. 249, 1921.)

eighth and ninth post-thoracic spinal roots). They conclude from this that in both spinal and decerebrate preparations,

"a single break shock, whether applied to a bared afferent nerve or to local skin, evokes, when the shock is considerably above threshold value, a reflex contraction which is both stronger and more prolonged than is the maximal twitch evoked from the motor nerve itself, and that is so whether or no the muscle retains its own intrinsic proprioceptive reflex arc. This excess of the reflex contraction over the maximal twitch indicates that summation of successive contraction-waves is present in the reflex contraction. So, further, does the occurrence, not unfrequent, of a more rapid up-gradient of tension development, despite less abrupt first onset of tension development, in the reflex than

in the maximal twitch. In other words repetitive discharge from the reflex centre occurs in response to a single induction shock stimulus applied to an afferent nerve or to local skin connected with that centre" (p. 116).

The technique employed in making the above observation did not permit of analysis of the "angle." In a later communication by Sherrington (*932*), in which the optical torsion-wire myograph was first utilized, reflex responses of the tibialis of spinal preparations were recorded optically and compared with the motor twitch. Many of the reflex responses such

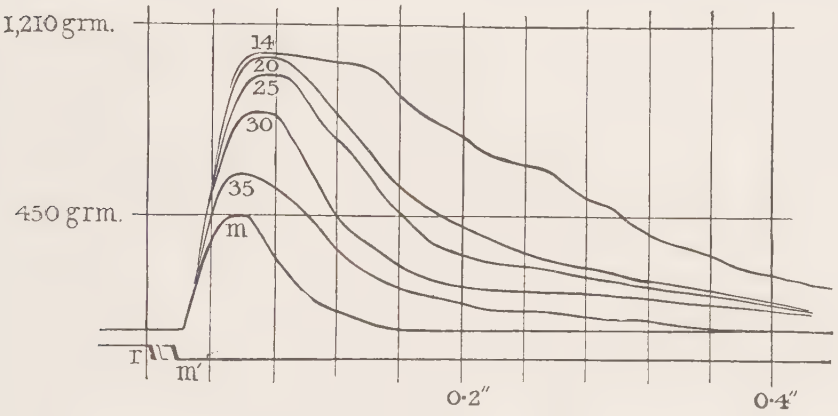

Fig. 113. Superposed tracings of photographic myograms of *tibialis anticus* of spinal cat, all from the same experiment, comparing those of greater crest-height than the maximal twitch, and indicating the change in the height and duration relation when the break stimulation to the afferent nerve (poplit.), is pushed to high strength, *i.e.*, 14 cm. The lowest curve (*m*) is the maximal twitch as given from 35 cm. up to 20 cm. The numerals opposite the other curves give the coil-distance of the break-shock for each; *tibialis anticus*, spinal cat. Time ordinates mark $\frac{1}{25}$ second: the drop of signal line at *r* shows latency for the weaker reflexes, at *m'* the latency for the motor twitches; the faint line of drop between these gives latency for the strongest reflexes. (Sherrington, *Proc. Roy. Soc.*, vol. 92B, p. 256, 1921.)

as those shown in figures 1 and 2 of his paper show relatively sharp angles, and these responses are of considerably greater duration than the motor twitches which are also shown. The existence in these records of an abrupt termination of the crest indicates, as already pointed out, that a large number of fibres have ceased contracting with approximate simultaneity. The increase of duration above that of a maximal twitch shows that these self-same fibres which have ceased contracting in unison must also have responded repetitively. Moreover, in some records, notably that

shown in figure 112 (from Sherrington's paper), undulations, which correspond both in shape and other mechanical characteristics to the secondary "angles" observed in the case of certain spinal knee-jerks, are to be observed during the period of relaxation, (*v. supra* fig. 106). It is probable that these are to be interpreted in the same way as were those of the knee-jerk, namely, that the undulations indicate the cessation of contraction in groups of fibres which have responded a larger number of times than those which ceased contracting at the angle. In figure 113 the superimposed tracings taken from Sherrington's photographic reflex myogram are reproduced and compared with the myogram of a motor twitch.

In reflex flexor responses observed by Fulton and Liddell (unpublished), in which the electrical and mechanical responses were recorded simultaneously, they observed that the "angle" may be exceedingly sharp even though the duration of the response was double or even triple that of the motor twitch. The electrical responses under these circumstances were similar to those of a knee-jerk of a spinal preparation,—that is to say they were single with a somewhat prolonged excursion below the base line. In none of these did we happen to obtain double responses, though in one evidence of rhythm could be seen in the diphasic portion of the excursion. The electrical and mechanical features of these responses therefore are in complete harmony with the observations and interpretations of Sassa and Sherrington (*845*) and Sherrington (*932*), that the simplest responses of the flexor reflex are repetitive in character.

A COMPARISON OF THE KNEE-JERK AND FLEXOR RESPONSES IN THE DECEREBRATE AND SPINAL CONDITION

Knee-jerks of decerebrate preparations, though more easily evoked than spinal jerks, are yet of shorter duration. The duration in fact is frequently merely that of a motor twitch. It may, however, be 50 or 80 per cent longer than a motor twitch and under such circumstances is probably a tetanus of 2 or 3 volleys of impulses. A spinal knee-jerk, on the other hand, is produced normally by at least 4 to 8 volleys of impulses. In respect of extent of volley repetition, therefore, the spinal knee-jerk is more ample than a decerebrate jerk. The latter appears, in other words, to be more "under control" than the spinal. It is therefore a point of great interest that Sassa and Sherrington found the reflex contraction of tibialis and other flexor muscles of the limb more readily evoked in the spinal preparation than in the decerebrate, and in the spinal animal the reflex contraction was more ample. In their size and duration, therefore both knee-jerk and flexor reflex are greater in the spinal than in the decerebrate condition. This is again in

harmony with the observations of Forbes, Cobb and Cattell (*329*) of immediate increase in size of the electrical responses of this reflex when the cord is severed (fig. 114).

These observations favour the view, well-established on other grounds, that the enhancement of these reflexes on being made spinal is a "release phenomenon." That it is not merely an irritative excitation from the recent wound is evidenced by its persistence not only for many hours, but, in experiments in which spinal transections were made aseptically for some days.

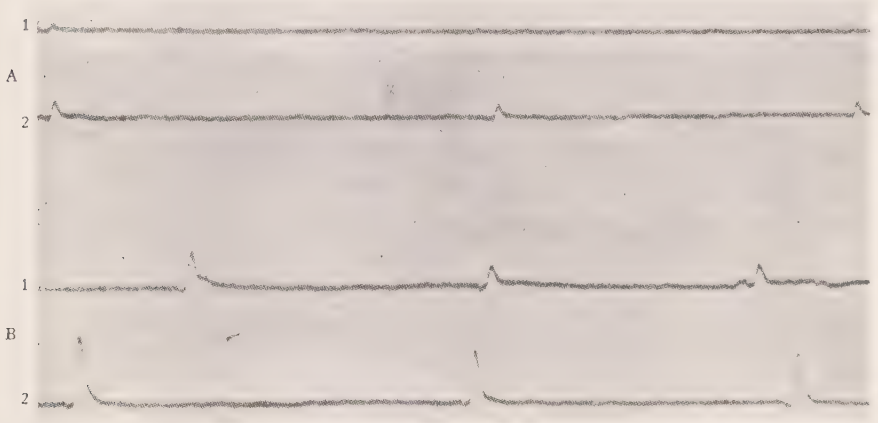

FIG. 114. Effect of spinal transection on reflex responses of the *nerve* to *tibialis anticus* to a series of stimuli, shown in two experiments, A and B. In each experiment, *1* is before transection; *2*, after. A rest of several seconds preceded the first stimulus of each series. Responses to break shocks only; make shocks subminimal. Electron-tube amplification in both experiments.

A. *1*, 14 minutes before transection; *2*, between 3 and 4 minutes after.

B. *1*, less than 1 minute before transection; *2*, 3 minutes after.

Speed of film 18.5 cm. per second. (Forbes, Cobb, and Cattell, *Amer. Journ. Physiol.*, vol. 65, p. 37, 1923.)

When the after-discharge of flexor reflexes in the decerebrate and spinal conditions are compared, it is found that the after-discharge of a decerebrate response may "tail off" for a considerable period even though the response is small. Under such circumstances the angles are usually not sharp. In the spinal response, which may be large and of considerable duration, the angles are usually sharp and the relaxation more abrupt. This indicates that in the spinal condition the motoneurones have a greater tendency to discharge the same number of times; while in the decere-

brate condition the number of discharges of the individual neurones probably varies widely.

SUMMARY

The knee-jerk, in whatever way elicited, is always produced by somewhat asynchronous volleys of impulses. In this respect it contrasts with motor nerve tetani, in which temporal dispersion in the beginning and cessation of activity of the participating elements is slight. Asynchronism, in the case of the knee-jerk, is evidenced by: (*a*) a less abrupt commencement of the rise of tension; (*b*) a more spread-out electrical response; (*c*) a higher point of inflection from convexity to concavity on the ascending portion of the knee-jerk curve; (*d*) a more modified "angle" (which is in turn followed by an initial concavity on the curve of relaxation) than are observed in motor nerve responses, where volleys of impulses are set up synchronously.

Significant differences have been found between the knee-jerk of decerebrate and of spinal preparations, the following being the most important. The *duration* of the spinal knee-jerk is two to three times greater than that of the decerebrate jerk, and the curve of relaxation of the spinal jerk is smooth, being without the "hump" which regularly occurs in a decerebrate jerk at approximately half-relaxation. In their electrical responses and in their latency, decerebrate and spinal jerks present but slight differences, the latency of the spinal jerk tending, however, to be greater than that of the decerebrate.

On the basis of the increased duration, it has been shown that the knee-jerk of the spinal preparation is a short tetanus composed of 4 to 8 volleys of impulses recurring at about 200 per second. The decerebrate jerk, on the other hand, has usually the duration of a single twitch, though under some circumstances it too may be a tetanus composed of two, and rarely three, volleys of impulses.

The "hump" characteristic of the decerebrate jerk has been termed the "myotatic appendage," and it is believed to be a manifestation of the "shortening reaction" of the tonic muscle.

The flexor reflex is, under most circumstances, also a short tetanus, even when elicited by a single break-shock. It possesses features in common with the knee-jerk, there being considerable temporal dispersion in the all-or-none responses of the participating units. Similar differences exist between the flexor reflex of decerebrate and of spinal preparations, as were found to obtain in the knee-jerks of such preparations.

Careful study of these relatively elementary reflexes has given important information concerning the nature of the central processes by which they are produced.

CHAPTER XII

Excitatory Reflexes in Response to Repetitive Stimulation: The Flexor and Crossed Extensor Reflexes Contrasted

According to the general law of reflex contraction established by Sherrington, Graham Brown (*168*) and others, stimulation of the central cut end of an afferent nerve supplying the hind limb of one side causes: (1) reflex contraction of the flexors on the same side, and inhibition of the extensors, and (2) contraction of the extensors of the opposite side and inhibition of the flexors. Several exceptions to this law have been noted and will be mentioned in the course of the chapter.

The crossed extensor reflex and ipsilateral flexor reflex differ fundamentally, and as it is essential for the reader to be thoroughly familiar with their differences, this chapter will concern itself with contrasting them.

It may be said at the outset of a discussion of such reflexes that the usual method of stimulation employed is unnatural, and, from the viewpoint of the *normal highly selective* character of afferent stimulation, is a radical departure from the way in which the centres of the nervous system are ordinarily excited. In stimulating the central end, *e.g.*, of the sciatic nerve, with repetitive induction shocks, it is impossible to distinguish between the functionally different groups of sensory units in the mixed nerve. Temperature, touch and pain fibres, and the fibres supplying the end-organs of muscular sense may all be stimulated indiscriminately. Despite this, however, the responses elicited by such stimulation are usually of the same general character, and have thrown much light upon the nature of reflex processes. It has been found, moreover, that responses evoked in this way are broadly similar to those evoked by separate excitation of several cutaneous pain fibres, *e.g.*, as by stimulating the pad of the foot by a stigmatic unipolar electrode. It is therefore permissible to examine the responses evoked by stimulation of mixed nerves, with a view toward elucidation of normal processes.

STIMULUS RHYTHM

Liddell and Sherrington (*636*, *637*) have recently studied, by an optical method of enhanced accuracy, the responses evoked in the flexor and ex-

tensor reflexes of spinal and decerebrate animals when the rate of repetition of stimulation is varied. For the flexor reflex they have employed both *semitendinosus* and *tibialis anticus*, and for the extensor reflexes, *quadriceps femoris*, or some part of this muscle.

Spinal reflexes. (*a*) *Ipsilateral flexor reflex.* In this reflex the stimulus rhythm was observed in the mechanical record of both of the muscles examined, at rates as high as 72 per second. At a stimulation frequency of 36 per second, removal of one stimulus during the reflex tetanus ascent caused a break in the ascent owing to the lapse of one step from the series. In the case of *tibialis anticus*, reflex tetani evoked by 90 break-shocks per second applied to the efferent nerve showed the rhythm just perceptibly in the mechanical record. These observations were confirmed electrically by Cooper and Adrian (*211*), who found that action currents were visible in flexor reflexes when stimulated at 90 per second and were also visible at even higher rates of stimulation, *e.g.*, 160 per second, which would cause complete fusion of a mechanical record. The presence of after-discharge was always evident in the mechanical record of these reflexes, but seldom in the electrical record, (*b*) *Crossed extensor reflexes* are not elicitable in the acute spinal preparation, and while they may be obtained from a "chronic" spinal preparation, the upper limit of stimulus rhythm has not yet been examined by an accurate method. Rhythms of 16 per sec. are, however, clearly visible in the myograph record (*638*).

Decerebrate reflexes. (*a*) *Ipsilateral reflexes:* (1) The *ipsilateral flexor* reflex shows an obvious tremor in the mechanical record up to 25 to 35 per second and is often still marked at 50 per second. The reflex may be readily inhibited by stimulation of any afferent nerve of the contralateral hind limb (*943*). During such inhibition, when the strength is not sufficient completely to extinguish the contraction, the reflex record still exhibits, both in its descent and in the floor of the inhibitory trough, contraction waves corresponding to the stimulus frequency. This suggests, as Liddell and Sherrington (*636*, p. 149) point out, "that under partial inhibition the reflex activation of a certain percentage of the involved muscle fibres—and therefore, since the inhibition is central, of the motoneurones of the centre—is suppressed, while that of the remainder continues seemingly unimpaired. The observations, in fact, support the suggestion by Keith Lucas and Adrian and also, with experimental support of other kind, by A. Forbes regarding the mode of operation of concurrent reflex excitation and inhibition in producing algebraical summation of effect." In the decerebrate responses of tibialis the rhythm is obvious only up to a frequency of 38 per cent, and in keeping with this the after-discharge tends in this muscle to be more marked than in semitendinosus. In both however, the after-discharge is considerably more marked than in the flexor responses.

(2) The *ipsilateral extensor reflex*, which has been studied by Sherrington and Sowton (*943*) and by Graham Brown and Sherrington (*168*), partakes of the characteristics of the ipsilateral flexor reflex: it develops quickly after a brief latency and subsides with very little after-discharge, and it reveals perceptible rhythm corresponding with the stimulus frequency even up to 90 per second (*364*). This suggests that fibres responding to the flexor reflex are intermixed with the fibres in quadriceps, for the reflex occurs even after both the sartorius and the tensor faciae femoris have been completely resected away. When a contralateral reflex is inhibited by an ipsilateral (inhibitory) stimulus, the ipsilateral extensor contraction may frequently be seen in the floor of the trough of the inhibitory relaxation. Owing, however, to the relatively slight after-discharge of this

reflex, it relaxes before the effect of the inhibitory stimulus on the contralateral reflex has ceased (see fig. 1, *364*). This gives rise to what has been termed the post-inhibitory notch (*639*). These ipsilateral contractions give rise in the trough of inhibitory stimuli to electrical responses corresponding to the rhythm of stimulation which account, as Fulton and Liddell have pointed out (*364*), for the so-called inhibitory rhythm in electrical records of inhibitory responses.

(*b*) *Contralateral reflexes*. The most convenient afferent nerve for the elicitation of the *crossed extensor reflex* of a decerebrate preparation is the peroneo-popliteal of the limb on the crossed side. Stimulus frequency in these reflexes is seldom detectable even at rates of 5 to 35 per second. At a rate of 49 per second excision of 3 consecutive stimuli does not alter the smoothness of the plateau, nor even does it check the smooth rise of the ascent. The ascent of such reflexes is gradual and of a wholly different character from those observed in the flexor reflexes (see figs. 115 and 119). Intercurrent inhibition, when weak, tends to bring out the stimulus rhythm of the excitatory reflex both in the descent and reascent of the reflex response.

Cooper and Adrian (*211*) have investigated the electrical responses of the crossed-extensor reflex, and have described what they have termed "primary" and "secondary" waves in the galvanometer record. The primary waves, when present, correspond with the rhythm of stimulation; the secondary waves, they attribute to asynchronous activity, probably in the nature of after-discharge. They observed in some preparations what they believed to be primary waves in response to stimulus frequencies as high as 60 per second. Fulton and Liddell (*364*) have recorded the mechanical and electrical responses of crossed extensor reflexes simultaneously, and have found the primary and secondary waves which Cooper and Adrian described, and have noted in addition that *primary waves are invariably associated with corresponding mechanical waves in the myograph record* (fig. 115). They infer from this that the primary waves represent large groups of fibres which respond more or less synchronously. They found that single inhibitory break shocks tend to enhance the size of the primary waves both in the string and in the myograph record. They attribute this unmasking of the primary waves to inhibition of repetitive after-discharge (see Chapter XIII; fig. 174, Chapter XVII). They found, other things being equal, that the primary waves were greater as the initial passive stretch of the muscle was increased. Inasmuch as the action currents of the muscle increase with the length of the fibres, they were inclined to attribute this augmentation in size of the primary waves largely to the peripheral apparatus.

In discussing the differences between the stimulus rhythm in various reflexes examined, Liddell and Sherrington (*636*, p. 153) have observed that,

"it is in the behaviour of the knee-extensor quadriceps femoris, in its decerebrate crossed reflex, that the outstanding divergence lies. In the other reflexes, which are all ipsilateral,

the fusion-frequency approximates to that of the tetani evoked by direct stimulation of the motor nerve itself. The factors which lead to this smothering of the stimulus

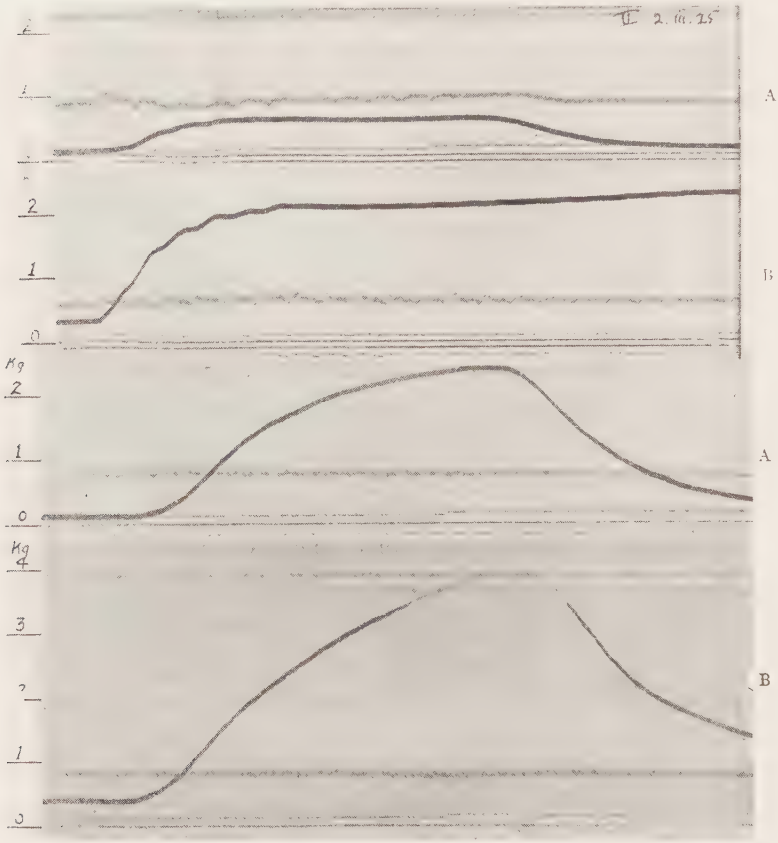

FIG. 115 A AND B. Crossed extensor reflexes of a decerebrate cat, taken at different initial tensions of the muscle to show alteration in magnitude of secondary waves. Stimuli, 14 per second at same strength in both responses. Time, 0.02 second. Upper signal, short-circuiting key. Note the general shape of the tension curve.

A. Initial tension, 100 grams.

B. Initial tension, 420 grams. (*364*)

FIG. 116 A AND B. Same as figure 115 from another preparation. In this the primary waves are smaller, which is reflected in the myograph by rhythm of stimulation being less marked. (*364*)

rhythm cannot attach to the afferent nerve fibres, for they presumably are the same in the case of all the reflexes examined. Neither does it lie in the motor nerve fibres and muscle fibres of the quadriceps itself; the character of the *mn.* [motor nerve] tetani establishes that.

The cause must therefore lie in the inclusion within the central path of the decerebrate crossed extensor reflex of some mechanism other than, and probably additional to, those included in the central path of the other reflexes examined. There is in the crossed decerebrate reflex of quadriceps extensor, so to say, a momentum of reaction—illustrated also by the prolonged after-discharge characteristic of this reflex—which tends to obliterate the stimulus rhythm, and even course fluctuations of that rhythm."

FEATURES OF THE MECHANICAL RECORDS OF SPINAL AND DECEREBRATE REFLEXES

The spinal flexor reflex (ipsilateral). The characteristics of the spinal flexor reflex, as exemplified by the contraction record of *semitendinosus*, a knee-flexor, and *tibialis anticus*, an ankle-flexor, in response to stimulation of the ipsilateral peroneo-popliteal nerve (or popliteal alone), are influenced by three circumstances: (1) the rate of repetition of the stimulus, (2) the intensity of the stimulus, (3) the degree of initial passive tension of the muscle at the time when the response. These three conditions influence the direct responses to motor nerve stimulation, as well as the reflex response, but the reflex responses of these muscles differ in certain important characteristics from the motor nerve responses. We will examine the motor nerve responses first.

In comparing motor nerve tetani with corresponding reflex tetani it is, of course, assumed that motor nerve impulses are identical in nature whether set up by discharge of the spinal centre or excited from a motor nerve axon. This is in keeping with the conceptions so well established by Lucas (*664*, *665*), Forbes (*318*, *15*) and Adrian (*15*, *19*, *3*). Grading of intensity of reflex contraction is accordingly controlled, as in the case of a motor nerve tetanus, by multifibre summation, *i.e.*, the number of motoneurones which the reflex activates, and by wave summation (Chapter IV), *i.e.*, the number of summed waves of contraction occurring in each individual motor unit.

Motor nerve tetanus. (1) Other conditions remaining the same the ascent-curve is steeper, the time of ascent less, the number of steps in the ascent higher and the ascent-plateau turn sharper, the greater the frequency of the stimulation (Chapter V). These features have already been observed in a previous chapter to characterize the responses of a motor nerve of a frog and need not detain us here. (2) In response to submaximal stimuli, other things remaining constant, the ascent-curve of a motor tetanus is shorter, the summation-number smaller, the ascent-plateau turn sometimes sharper than in response to maximal tetani. These observations are in keeping with the results of tetanic stimulation of the lumbar roots supplying the gastrocnemius of the frog (Chapter VI). (3) Increase within limits of

the initial passive stretch (length of fibre) increases, as we have seen, the tension developed in response to single-shock or to tetanic stimulation. This results from the fact that as the fibre length increases the energy liberation, stimulus for stimulus, becomes augmented. Also the greater the initial stretch the steeper the ascent, the longer the duration of the ascent (and therefore the greater the summation-number), and the more gradual is the ascent-plateau turn.

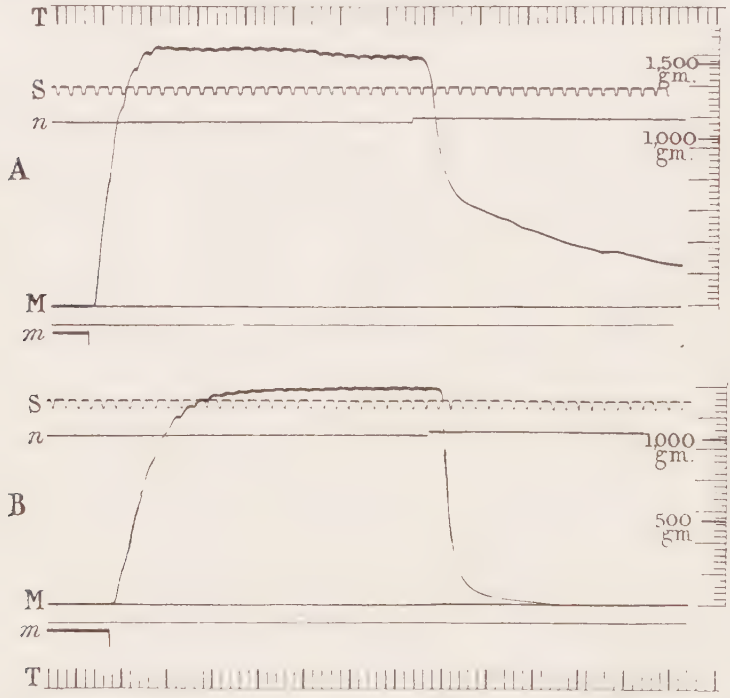

FIG. 117. *Semitendinosus.* A, reflex tetanus, spinal preparation, afferent nerve ipsilateral peroneo-popliteal.

B, motor-nerve tetanus, in same preparation as yielded A.

In both break-shocks at 38 per second. *T*, in 0.02 second. Tendon movement × 35. (Liddell and Sherrington, *Proc. Roy. Soc.*, vol. 95B, p. 146, 1923.)

Reflex tetani. The reflex responses of these muscles are influenced by the three conditions just enumerated just as are the motor nerve responses. One may therefore consider the *differences* between the reflex and the motor nerve responses. In comparing one with the other it is desirable that all conditions should be similar for both. The initial tension of the muscle and rate of stimulation are easily controlled, but for stimulus intensity there is no

accurate basis of comparison, since the thresholds for reflex stimulation are different from those of motor nerve stimulation. For want of better criterion one must, therefore, compare responses in which comparable tensions are developed. This is scarcely an adequate basis of comparison in one sense, for owing to the tendency toward after-discharge greater tension would be developed by the participation of fewer fibres than is developed in motor nerve responses. When compared in this way, however, the differences generally observed may be summarized as follows (fig. 117). (1) The initial step in the ascent (*i.e.*, the first contraction) of reflex tetani is almost invariably higher than the initial step in the motor nerve response, (2) the slope of the ascent is in the majority of records examined by Liddell and Sherrington (*637*) steeper than in the motor nerve response, (3) stimulus rhythm is less clearly visible in the mechanical record of the reflex response than in that of the motor nerve, (4) the reflex response subsides less rapidly, and (5) a frequent difference between the reflex tetanus and motor nerve tetanus, especially in response to weak stimulation, is that the plateau of the former, instead of remaining parallel with the base line, tends to decline slightly as it progresses.

Since a small amount of repetitive after-discharge occurs in a flexor reflex even in response to a single break shock stimulus, after-discharge suggests itself as the cause of the divergencies between the reflex and motor responses. Thus the steeper ascent of the reflex response would be difficult to explain on any other basis than that of after-discharge, as would also the greater tendency toward smothering of the rhythm of stimulation in the mechanical record. The greater height of a first response of the reflex tetanus was investigated by Liddell and Sherrington (*637*) by comparing what they designated as a single-shock/tetanus ratio in the reflex and motor nerve responses. Denoting these ratios as *ss/tet reflex* and *ss/tet mn* (motor nerve), they found that the *ss/tet reflex* is rarely as low as 40 per cent, being in some responses as high as 70 and 80 per cent (fig. 118). Since in many cases these single shock reflex responses were larger than maximal motor nerve responses, the explanation of these ratios again must lie in the occurrence of repetitive after-discharge. Moreover, if the duration of the single shock responses in Liddell and Sherrington's published curves are measured it will be found that the reflex responses have a duration lying between 60 and 100σ, whereas the motor nerve responses are 40 to 45σ in duration. In view of the facts brought forward in the previous chapter this too provides clear evidence of the repetitive character of these "single" responses.

One may conclude from the comparison of these reflex flexor responses

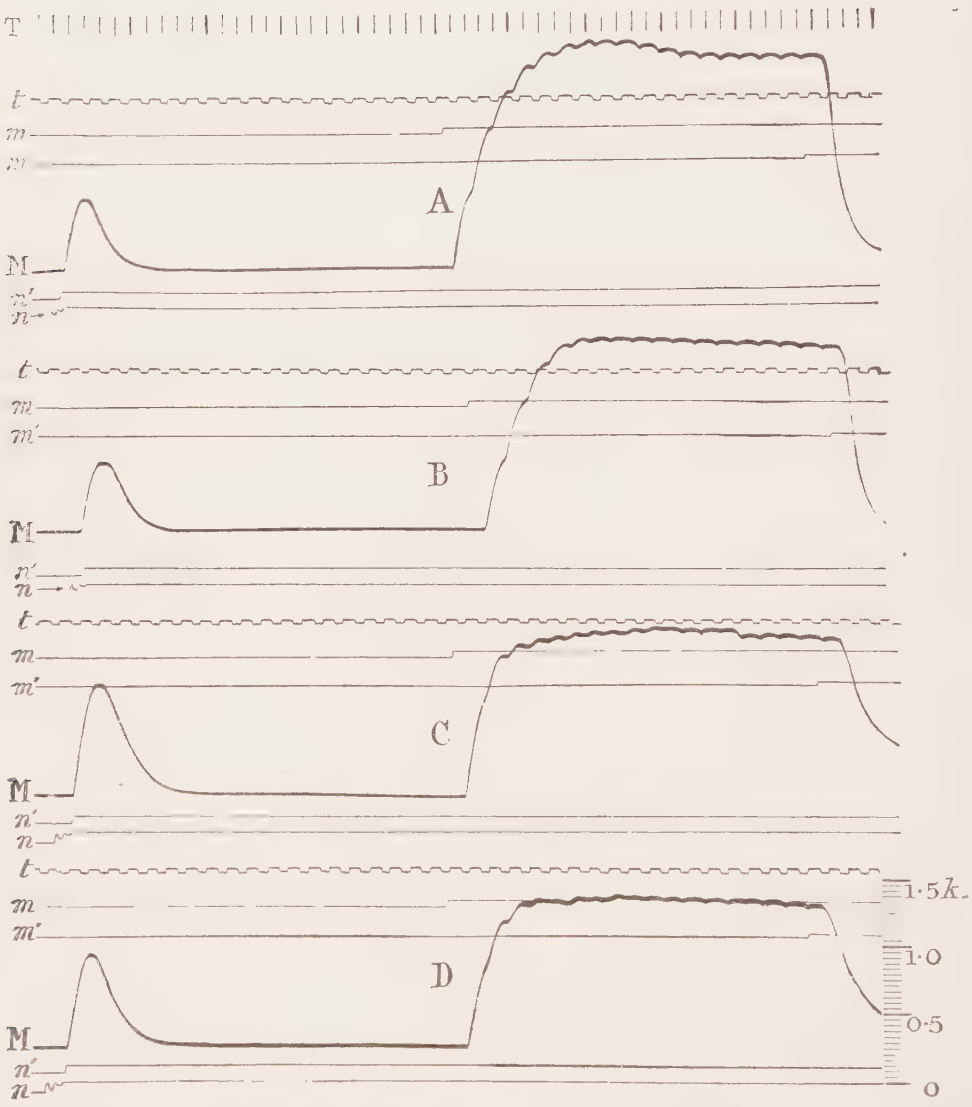

FIG. 118. *Tibialis anticus*, single-shock/tetanus ratio, showing that the single shock response is much higher in the reflex than in the twitch, proving the existence of wave summation in the former. A and B, motor nerve stimulated, coil at 18.5 cm. in A, 21 cm. in B. C and D, reflexes, ipsilateral popliteal nerve, coil at 13.8 cm. in C, at 14.5 cm. in D. In C the initial passive tension (stretch) rather greater than in rest. Stimulation frequency 39 per second. *T*, 0.02 second. Myograph magnification of tendon movement 60 times; tension calibration on D for all. (Liddell and Sherrington, *Proc. Roy. Soc.*, vol. 95B, p. 313, 1923.)

with those of the corresponding motor nerve responses that in the ipsilateral spinal flexor reflex the reaction to a repetitive stimulus of constant frequency and intensity "engages initially a number, greater or smaller according as the stimulus is stronger or weaker, of the totality of the motoneurones passing to the muscle, which initial number is from the very outset the full quota of the totality of the muscle's motoneurones which the reflex will, under continuance of that stimulus, engage." (2) The initial number so elicited does not increase and in some responses progressively diminishes, *i.e.*, motoneurones once engaged appear in some responses to slip away from the grasp of the exciting reflex. This, as Forbes, Cobb and Cattell (*329*) have suggested may be due to the fact that the excitatory stimulus, as the response progresses, finds an increasing number of neurones engaged in after-discharge, and hence incapable of further response; but if they are so engaged it is difficult to understand why the response should diminish. These features have been found to occur in response to skin stimulation, as well as to direct stimulation of the afferent nerve, and therefore cannot be attributed to anything inherent in the unnatural character of the latter method of stimulation. (3) The magnitude of the reflex response at constant initial tension of the muscle is conditioned entirely by the intensity of stimulation. Continuance of the stimulus, in other words, does not enlist as it progresses an increasingly large number of motoneurones.

CROSSED EXTENSOR REFLEX (DECEREBRATE)

Mechanically this reflex is characterized by the following features (fig. 119): (1) A long latency: 50σ, as contrasted with 8 to 10σ, the latency of the flexor reflex. (2) The stimulus frequency may not be seen in the reflex even when the rate of stimulation is as low as 5 per second and it is usually not seen at rates of stimulation above 20 per second; therefore, no summation-number can be assigned to the ascent of the reflex. (3) The duration of the ascent is often 5 to 10 times or more greater than that of the flexor reflex. (4) The form of the ascent differs markedly from that of the flexor reflexes, being commonly sigmoid, that is, it commences gradually in an initial concave upper portion and then after attaining its steepest gradient it becomes less steep on approaching the plateau. Not infrequently, however, the sigmoid character is departed from; *e.g.*, one often observes an ascent occurring in steps, the first step of which is usually abrupt (fig. 119, B and C), and after a short plateau the second step commences more gradually. Another variety of ascent is a rectilinear gradient which may climb steadily throughout a period of 3 or 4 seconds.

These divergencies from the form exhibited by the flexor reflex cannot be

attributed to anything inherent in the nature of the extensor muscle, for the motor nerve response of the *quadriceps* is similar in almost every detail

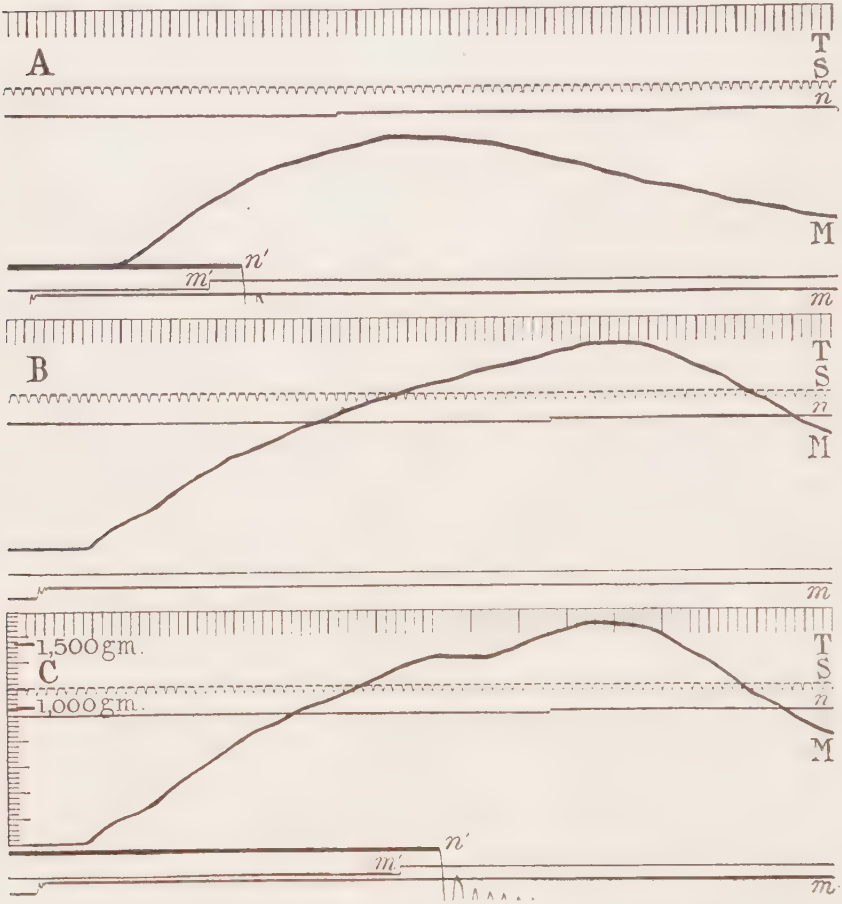

FIG. 119. Decerebrate crossed extensor reflex of *vasto-crureus*. Afferent nerve contralateral peroneo-popliteal; break-shocks, 48 per second. In A, lapse of three successive stimuli between marks given by short-circuiting signals m′ and n′. In C, lapse of four (? five) successive stimuli. B, stimulation the same as in C, but without any lapse. The tension scale applies to A and B as well as C. *T*, 0.02 second. Note two stepped ascent in B and C. (Liddell and Sherrington, *Proc. Roy. Soc.*, vol. 95B, p. 151, 1923.)

to that of the flexor muscles (figs. 120 and 121). The motor nerve responses of quadriceps, moreover, are modified by the three conditions of stimulus frequency, intensity and initial stretch of the muscle, as in the case of flexors.

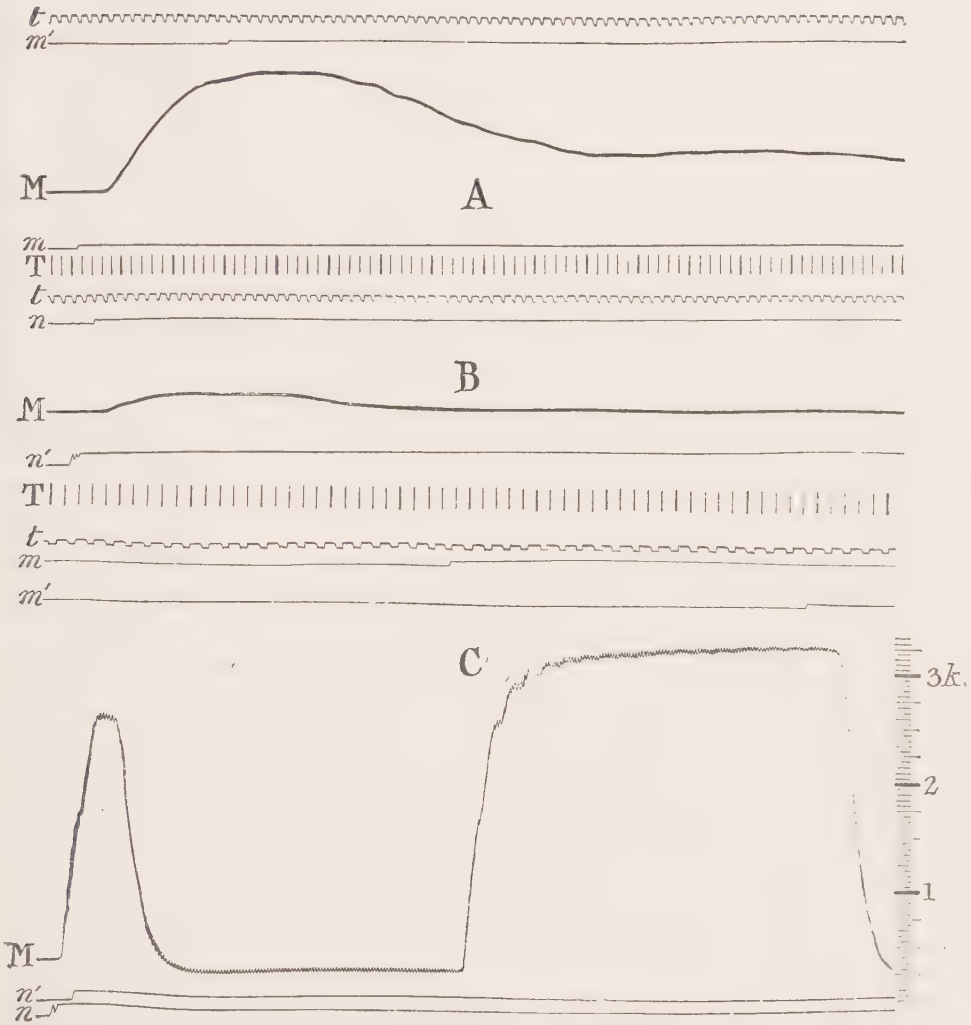

FIG. 120. Crossed extensor reflex of *vasto-crureus*. Contralateral peroneo-popliteal nerve; consecutive obs., coil at 16 cm., frequency 49 per second.

In A, thirteen shocks delivered, in B two (? three) shocks. B's contraction tension about 13 per cent of A's.

C. *Vastus externus:* motor nerve stimulation, coil 18.5 cm., frequency 38 per second, delivery of two shocks followed by series of 19. Two-shock reaction develops a tension about 80 per cent of tetani plateau tension. *T*, 0.02 second; small vibrations in myograph record = $\frac{1}{25}$ second. Calibration scale of tension at side, in kilograms. (Liddell and Sherrington, *Proc. Roy. Soc.*, vol. 95B, p. 332, 1923.)

The initial passive tension of the muscle appears to have an even greater effect upon the response than in the case of the flexor reflex, this being true of the reflex as well as the motor nerve reaction (fig. 122). *The divergence in the form of this reflex from that of the motor nerve tetanus must therefore lie in the reflex mechanism.* Increase of stimulus frequency shortens the latent period of the crossed reflex and increases the steepness of the ascent, acting therefore in much the same way as in the flexor reflexes. In the same way increase of stimulus intensity causes the latent period to be shortened,

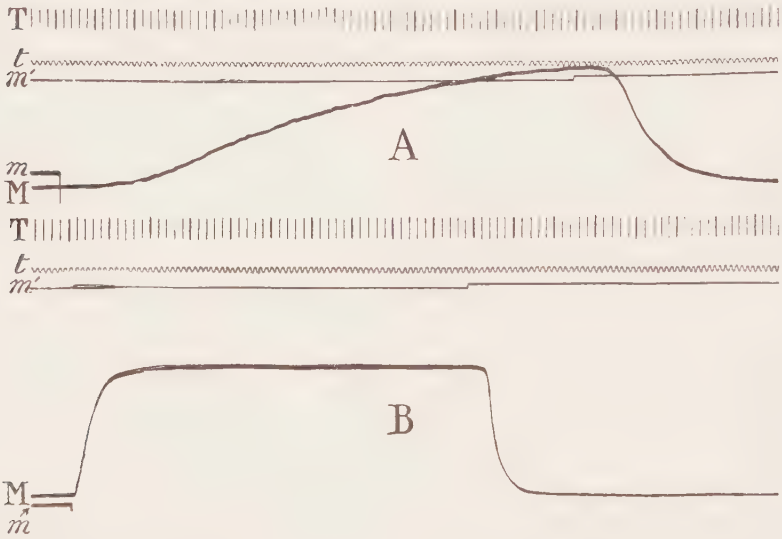

FIG. 121. The crossed extensor reflex of quadriceps compared with the motor nerve response of that muscle.

A. Reflex contralateral peroneo-popliteal nerve stimulation, coil 14.5 cm., frequency 38 per second.

B. Motor nerve stimulated, coil 22 cm., frequency 38 per second. *T*, 0.04 second. (Liddell and Sherrington, *Proc. Roy. Soc.*, vol. 95B, p. 321, 1923.)

the ascent to become steeper and higher and plateau tension to become enhanced.

"*Recruitment.*" The characteristics of the response of quadriceps in this reflex admit of certain important inferences. It is evident that at the commencement of the crossed extensor response the number of neuro-muscular units engaged is small, but mere continuance of the same stimulus, unaltered in intensity, causes a progressively large number of muscle fibres to be brought successively into activity. This accrescent process has been termed "recruitment" (*637*, p. 335). Experimental evidence favouring this

interpretation of the mechanical ascent is provided by the fact that discontinuance of the repetitive stimuli for a short interval during the mechanical

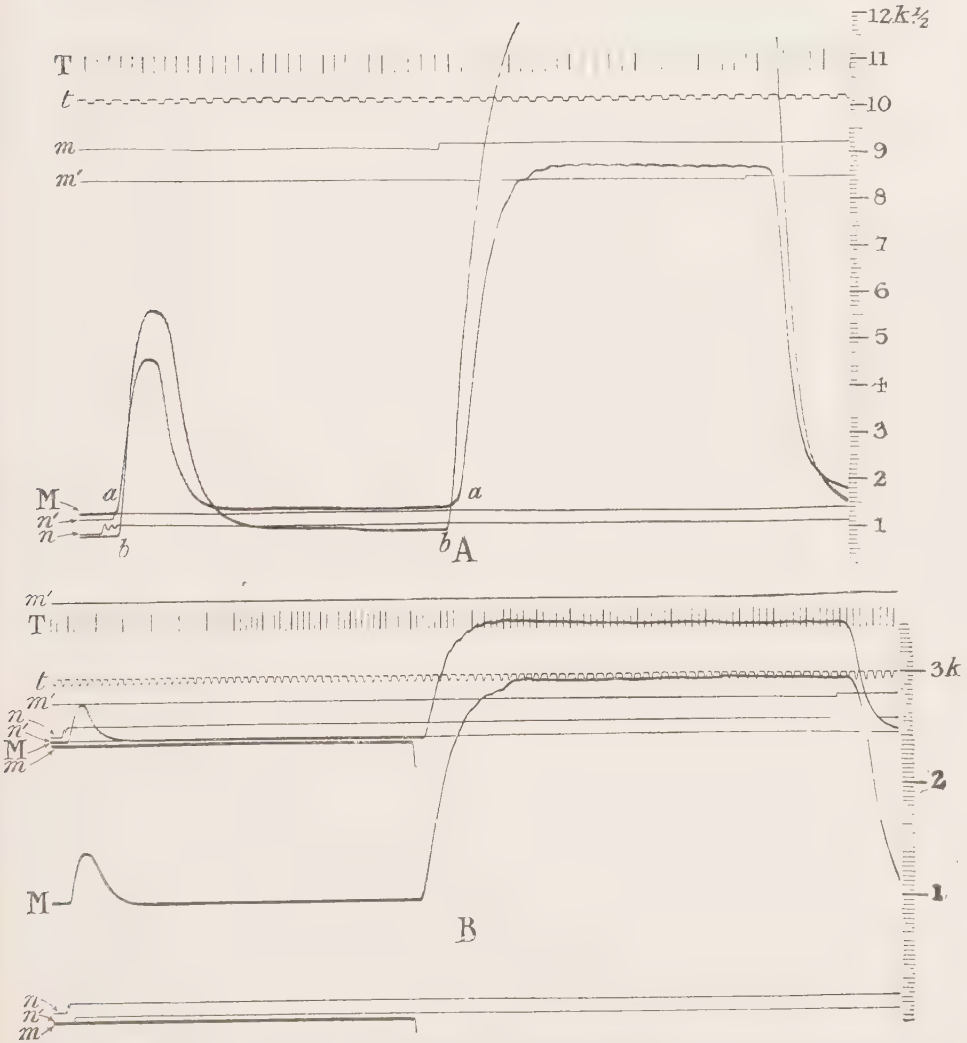

FIG. 122. *Vasto-crureus*. Showing the effect of initial length upon the size of the response. Motor nerve, stimulated, approximately maximal, coil 19 cm., frequency 38 per second. For curve *b* initial stretch of muscle increased by 6 mm. Total length of muscle 93 mm.: magnification of tendon movement by myograph 162; tension calibration in 0.5 kgm. at side; weight of cat 2850 grams. *T*, 0.02 second; small vibrations in myograph, $\frac{1}{250}$ second. (Liddell and Sherrington, *Proc. Roy. Soc.*, vol. 95B, p. 322, 1923.)

ascent leaves all the motoneurones which have already been activated by the reflex still actively engaged in the discharge of impulses. When a lapse of 0.1 second was made to occur, a check resulted in the ascent but in that short time the tension did not sink below the level already attained. Figure 119 shows such an experiment and it will be seen that after the stimuli are allowed to lapse the tension rises for a period roughly equivalent to the latent period of the reflex and then runs horizontal at the attained level. Upon renewal of the stimulus, motoneurones already activated will still be engaged in the discharge originally evoked by the external stimulus, but they are "now self-operated by the central mechanism." It is evident from this experiment that the external stimulus, if continued during the period in which it had been allowed to lapse, would have found all the motoneurones (participating in the response at the moment of lapsing) actively engaged in repetitive after-discharge. As Forbes, Cobb and Cattell have pointed out, it would be impossible to provoke in these actively discharging neurones any further responses. It follows accordingly that on finding a proportion of neurones already in activity, the external stimulus gradually enlists more and more inactive neurones. This process of recruitment, though present in spinal extensor reflexes, has not been detected in spinal flexor reflexes (*637*). It is clear, therefore, that mere prolongation of a stimulus of unaltered strength is a factor in the *intensity* of the crossed extensor reflex *but not in the flexor reflex.*

The recruitment process, which thus characterizes one type of reflex and not another, is certainly not attributable to differences in the afferent fibres employed for excitation of the two, since the same afferent nerve is used for both; that recruitment does not arise from the motoneurones themselves, or at least from their axons, is evident from the fact that recruitment does not occur in the knee extensor's ipsilateral spinal reflex. A further difference between the two lies in the fact that the crossed extensor reflex is favoured by the decerebrate condition and it would appear, in view of the marked influence which the hind-brain exerts on this reflex, that recruitment is conditioned by an interplay between the spinal centres and the hind-brain. We shall see presently that the recruitment process is also favoured by the integrity of the proprioceptive nerves; consequently the recruitment process must similarly be modified and conditioned by proprioceptive impulses.

The decerebrate crossed extensor decerebrate reflex exhibits characteristics which Sherrington has figuratively termed "inertia" and "momentum." The process of recruitment is clearly analogous to inertia, that is, it commences gradually and little by little acquires greater speed of move-

ment and in so doing acquires the power of continuing its activity after cessation of the force which set it into motion,—that is to say, it develops after-discharge (momentum). Recruitment itself, however, is always absent from true after-discharge. The influence of inhibition on recruitment and on after-discharge will be dealt with in the following chapter.

Liddell and Sherrington point out that rhythmic contraction of the fully isolated and deafferented vastocrureus exhibits in spontaneous stepping a sigmoid ascent and all the other characteristics of a recruitment process. This suggests that the sigmoid form, and the recruitment of which it bears evidence, is a normal feature of this phase of rhythmic contraction necessary to locomotion.

We cannot deal here with the interesting modifications of the crossed extensor reflex observable in thalamic preparations (see Girndt, *396*, and Girndt and Schaltenbrand, *397*). It may be noted, however, that the reflex is of the same general character, though of shorter duration, and that it exhibits a greater tendency to be "monophasic" *i.e.*, to be without rebound contraction.

REBOUND CONTRACTION

Early in the investigation of reflexes of decerebrate animals, it was observed that when strong stimuli are applied to an ipsilateral afferent nerve, either during a background of crossed extensor contraction, or during a background of slight or negligible tonic activity, there follows at a short interval after cessation of the inhibitory stimulus a spontaneous contraction of the extensor muscles (fig. 123). The size of the contraction, other things being equal, usually increases with the strength of inhibitory stimulation. The phenomenon has been thoroughly investigated by both Sherrington (*905*, *907*, *911*, *914*, *925*) and T. Graham Brown (*160*). They find it to be somewhat fickle phenomenon, being in some preparations difficult to observe, and often in the same preparation it appears and disappears again without apparent reason. The following are the more important features which have thus far been ascertained concerning this type of contraction. (1) It occurs in decerebrate and thalamic animals (*396*), and to a less extent in spinal preparations (*160*). (2) It is easily inhibited and the characteristics of its inhibition closely resemble those of the inhibition of plateau after-discharge (*641*). (3) It occurs in deafferented muscle. This fact, which was first shown by Sherrington, was observed in a preparation in which posterior roots 4, 5 and 6 had been severed (which removes completely the afferent supply of quadriceps). The inhibitory stimulation then passes through roots 7 and 8 (*919*, *160*). (4) The electrical responses

during rebound have been recorded by several observers (*319*, *364*), and have been found indistinguishable from the string record of plateau after-discharge; that is to say, small vibrations occur at a high rate, the rate being determined by the mass of the galvanometer string (*319*). (5) Rebound occurs most readily in response to strong stimulation of a bare afferent nerve. It has seldom been observed in response to a "natural," that is to say, a homogeneous group of purely inhibitory impulses. Thus,

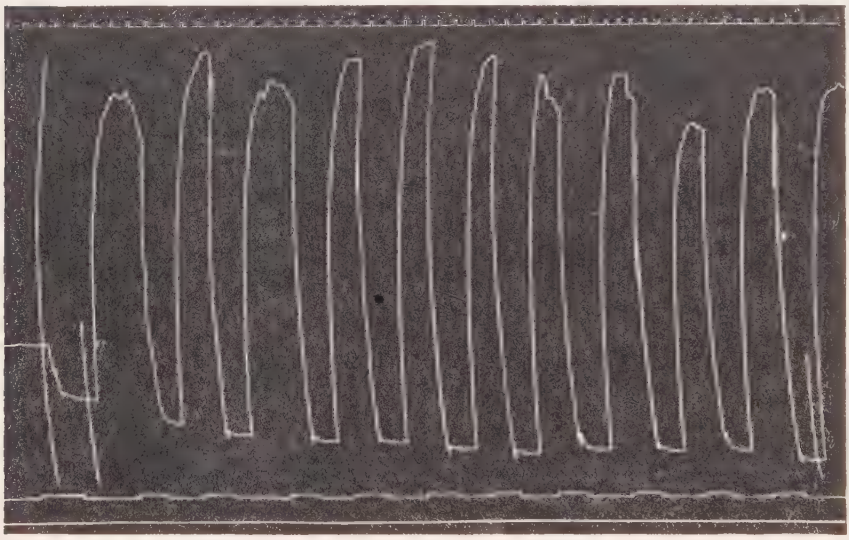

FIG. 123. Rebound: isolated extensor muscle. On applying the electrical stimulation (first rise of the signal line) to the foot-nerve, the myogram line falls and remains down during the stimulation, showing the reflex inhibition of the tonus. After 3 seconds the stimulus is discontinued (fall of the signal line); a post-inhibitory rebound contraction ensues during this discontinuance of the stimulation. This contraction is then cut down by reapplication of the stimulus (second rise of signal line), the muscle being again relaxed by inhibition. On withdrawal of this stimulation a rebound contraction re-ensues. This is repeated eleven times, each lapse of the stimulus giving an active extension of the knee. Decerebrate cat. Time marked above in seconds. (Sherrington, *Quart. Journ. Exper. Physiol.*, vol. 6, p. 279, 1913.)

Liddell and Sherrington (*640*), when inhibiting the stretch reflex by applying tension to the opposed flexor muscle did not observe rebound following the inhibition even though in many cases the inhibition produced rapid relaxation.

These features of rebound contraction permit one to draw certain conclusions. The fact that it occurs only with difficulty in the spinal animal

(*160*) shows that the phenomenon is favoured by the integrity of the higher centres, and it is clear from the experiments on deafferentation that the contraction is purely spontaneous and that it does not necessarily originate in proprioceptor activity. The fact that it is easily inhibited suggests, but does not prove conclusively, that the motoneurones responsible for the contraction lie downstream in the reflex arc because the contraction does not appear to be supported by concomitant excitation such as might occur from the higher centres. Moreover, the fact that the locus of inhibition is, in all probability, in the motoneurones immediately supplying the muscles of the quadriceps suggests that it is in the intrinsic activity of these self-same motoneurones that rebound contraction originates.

Two explanations for the occurrence of rebound contraction may be urged. The fact that it does not occur when a homogeneous group of inhibitory impulses is set up suggests that the cause of it lies in the method of stimulation by which it is ordinarily elicited. It is known that the mixed afferent nerve of an ipsilateral limb, though the predominant effect of stimulation is inhibitory to the extensors, also contains fibres which cause ipsilateral excitation of extensors. Sherrington and Sowton (*942*), for instance, observed that by altering the character of the stimulus applied to the ipsilateral nerve, one could at will provoke either reflex contraction of quadriceps or reflex inhibition. Rheonome currents of long duration and slow rise maximum (*i.e.*, long chronaxie) led to reflex contraction. On strong stimulation of the nerve, both of the functionally different groups are undoubtedly stimulated. Now it is known that an inhibitory stimulus leads to inhibitory after-discharge in exactly the same way as excitatory stimulation leads to excitatory after-discharge (Chapter XIII). It might, therefore, be urged that rebound contraction results from the after-discharge of excitation outlasting the after-discharge of reflex inhibition. This is substantially the view put forward by Sherrington and Sowton (*942;* also an unpublished communication). Though attractive there are certain (probably unimportant) objections to this view, one of which is that such ipsilateral contractions of quadriceps as have been observed are characterized by notably short after-discharge. This, however, might conceivably be due to inhibition of that after-discharge, the inhibition being unable to quell completely the supported excitation.

Another suggestion has been offered, namely, that rebound contraction is comparable to the so-called "*closing* tetanus" which occurs when constant currents are passed through the motor nerve in experiments on kataelectrotonus and anelectrotonus. After prolonged depression of activity, according to this view, the protoplasm of the nerve fibres in one case and in the motoneurones in the others respond by a period of activity. Neither

explanation seems fully adequate and the causation of this phenomenon must therefore be left unsettled. The former, however, is substantiated by more direct experimental evidence.

Mechanically, the ascent of a rebound contraction displays usually a sigmoid character which indicates that a recruitment process lies behind the development of the response (*641*).

The significance of rebound, and of successive spinal induction of which rebound is a manifestation (*910*), as a factor in the coördination of movement, has been dealt with at length by Sherrington (*925*), and is discussed below in Chapter XVIII.

SUMMARY

Recent accurate myographic analyses of the flexor and extensor reflexes of decerebrate and spinal preparations have revealed new and important information concerning the way in which these responses are integrated by the central nervous system.

The flexor reflex is typical of a group of central nervous reactions which is characterized by this feature, namely, that the number of centrally responding motoneurones is determined by the number of afferent nerve fibres stimulated, and there occurs no progressive increase in the number of excited units during the time that the stimulus is continuously applied. It is a *reaction d'emblée*, and in this respect the flexor reflex resembles a motor nerve response. But, from a motor nerve response, the flexor reflex is distinguished by virtue of its extensive after-discharge, which is more pronounced in decerebrate than in spinal preparations.

In contrast to the flexor response, the extensor reflex is characterized by *recruitment;* that is, under mere continuance of an unaltered stimulus applied to an afferent nerve, the number of motoneurones participating in the reaction progressively increases, so that continuance of stimulation becomes a factor in the *intensity* of the response, while in the flexor reflex continuance of stimulation causes no more increase in the response than would occur in a motor nerve tetanus.

The rhythm of stimulus may be seen in the mechanical response of the spinal flexor reflex at rates as high as 72 per second. Owing, however, to the more extensive and more asynchronous after-discharge, and owing also to the recruitment process, the rhythm of stimulus is seldom observed in the crossed extensor reflex at rates higher than 5 to 20 per second, and is sometimes not even observed at these low rates.

Rebound contraction is discussed and the theories which have been put forward to account for it considered. The theory which regards it as due to simultaneous stimulation of excitatory and inhibitory fibres in the afferent nerve, the excitatory fibres having more prolonged after-discharge, is regarded as the most adequate.

CHAPTER XIII

Central Inhibition

Recent development of the theories of central inhibition renders desirable a detailed examination of the behaviour of the inhibitory process as a basis for critical examination of the theories which have been offered. Such a detailed study has recently been made by Liddell and Sherrington (*641*), and the facts about to be set forth are drawn largely from their work. The electrical responses of active muscles subjected to varying degrees of inhibition have been investigated by Beritoff (*70a*), Adrian (*9*), Fulton and Liddell (*364*) and others (*252*, *269*), but these investigations have thrown less light upon the nature of inhibitory process than have those in which mechanical responses have been examined by an accurate method.

The usual way in which the central inhibitory process is studied is by recording the effect of an inhibitory stimulus which falls during a pre-existing "background" of reflex contraction. Thus in a highly tonic muscle, postural contraction may be used as a background and its relaxation examined in response to single or repetitive inhibitory stimuli. The most fruitful results have, however, been obtained by using a background of the crossed extensor reflex. The muscle ordinarily selected for this purpose is the quadriceps extensor of the knee. It has the double advantage of being highly "tonic" when in the decerebrate condition, and of responding readily to contralateral stimulation by active contraction (crossed extensor reflex). The quadriceps muscle in addition may be used for the elicitation of the knee-jerk, the inhibition of which can also be studied. For eliciting the crossed extensor reflex one of three nerves are generally used: the internal saphenous which is composed entirely of afferent cutaneous fibres, the hamstring nerve which is purely a muscle nerve, or the peroneo-popliteal, which is a mixture. For producing inhibition one has the same choice of nerves, on the ipsilateral side. Generally speaking the hamstring nerve, since it supplies the antagonistic flexor muscles, is somewhat more effective as an inhibitor than either of the others.

The "locus" of inhibition (*636*, p. 153)

Since inhibition, when complete, implies complete cessation of mechanical activity, it might be thought that mere cessation of reflex stimulation would

be equivalent to inhibition, but this is clearly not the case in responses in which extensive after-discharge occurs. In figure 124 the effect of lapsing 6 consecutive excitatory stimuli in a break-shock series of 49 per second is compared with stimulation of an inhibitory afferent nerve for a somewhat briefer period. Actually the inhibitory stimuli were only 3 or 4 in number. Now a lapsing of 6 excitatory stimuli means complete absence for that

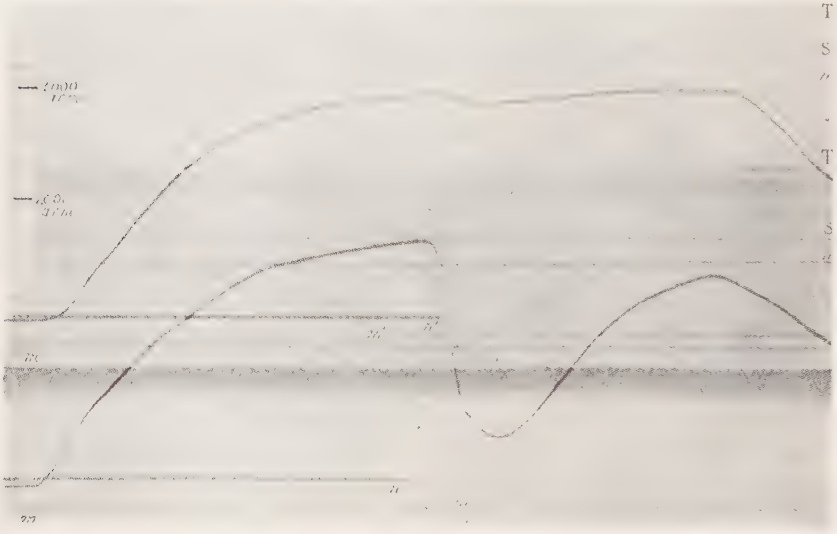

FIG. 124. *Vasto-crureus*, decerebrate: reflex tetanus from crossed peroneo-popliteal nerve by break-shocks at 48 per second. Same intensity of stimuli for both reflexes; in the upper a lapse of six consecutive stimuli during short-circuit marked by signals m′ and n′; in the lower no lapse of the stimuli to the excitatory afferent nerve, but an inter-current faradisation of the ipsilateral peroneo-popliteal nerve for the period marked between signals n′ and m′, a period corresponding to the delivery of three consecutive stimuli to the contralateral afferent nerve. Time, $\frac{1}{5}\frac{1}{0}$ second. Same tension scale applicable to both curves; intensity of stimuli for both, 15 cm. secondary coil. Intensity of stimulation to inhibitory nerve, 16 cm. secondary coil. Tendon movement × 35. (Liddell and Sherrington, *Proc. Roy. Soc.*, vol. 95B, Pl. 8, 1923.)

period of all afferent impulses, and therefore it clearly affects all the motoneureones involved. The figure shows that absence of these 6 stimuli has caused only a shallow notch of 100 grams in a plateau tension of 1900 grams. The reflex inhibition on the other hand, operating during an even shorter period reduced a plateau tension of 1900 grams by 1400 grams in 0.06 second and during the next 0.08 second by a further 200 grams—and this during continuous stimulation of the excitatory nerve. In other similar

experiments, described by Liddell and Sherrington (*636*), 8 stimuli of a series applied to the afferent nerve were excluded, and as a result of this, a tension of 2000 grams only became diminished to 1800 grams, while reflex inhibitory stimulation for a similar interval caused a response of 1800 grams to fall to zero in 0.15 second. It is evident from these observations that inhibition acts *at some point of the central mechanism further "down-stream" in the reflex arc than the terminal fibres of the excitatory afferent nerve, and at some point beyond the seat of momentum, i.e., beyond the point of origin of the after-discharge.* In view of its time relations and very short latency, as determined by inhibition of the knee-jerk, it is likely that the seat of the inhibitory effect is chiefly in or around the motoneurones directly supplying the muscle fibres of quadriceps,—in the region of the so-called "final" motor neurones.

INHIBITION OF THE KNEE-JERK

Sherrington, as we have seen, was the first to show that the "spinal" knee-jerk is an inhibitable phenomenon (*875*), and it was this discovery (1893) which caused the reaction to be regarded by many investigators as a reflex similar in nature to the other well-recognized spinal reflexes. To elicit inhibition, Sherrington used, among other agents (see Chapter XI), repetitive induction shocks applied to an ipsilateral nerve. He noted that the period of inhibition considerably outlasted the duration of the inhibitory stimulus, and he also observed that after recovery there followed a period of enhanced excitability during which the knee-jerks were of larger size than usual (*910*, p. 89). In endeavouring further to analyze the after-effects of inhibitory stimuli, Ballif, Fulton and Liddell (*48*) used single break-shocks for producing inhibition. The usual method employed was to elicit a series of knee-jerks in a spinal or decerebrate preparation at a rate of approximately 3 per second. The inhibitory stimuli in successive records were so timed as to fall at various points before or after a knee-jerk, and the moments of stimulation could then be plotted on a time scale. Great differences were found in the susceptibility to inhibition of knee-jerks of spinal preparations on the one hand, and of decerebrate preparations on the other.

The spinal knee-jerk. When an inhibitory stimulus of moderate intensity falls during a series of spinal knee-jerks recurring at 3 per second, as many as 1 to 6 successive jerks may be completely inhibited. Following the period of complete inhibition of the jerks, there occurs a period of partial recovery during which successive knee-jerks are of sub-normal but of progressively increasing size as they occur later and later on the time scale.

The period of recovery may be plotted graphically in terms of percentage height (ordinates), *i.e.*, tension, of a normal jerk. The size of a "normal" jerk was found to be constant, under the method of elicitation employed, within 5 per cent. A graph illustrating recovery of the spinal knee-jerk from a single inhibitory shock is shown in figure 125.

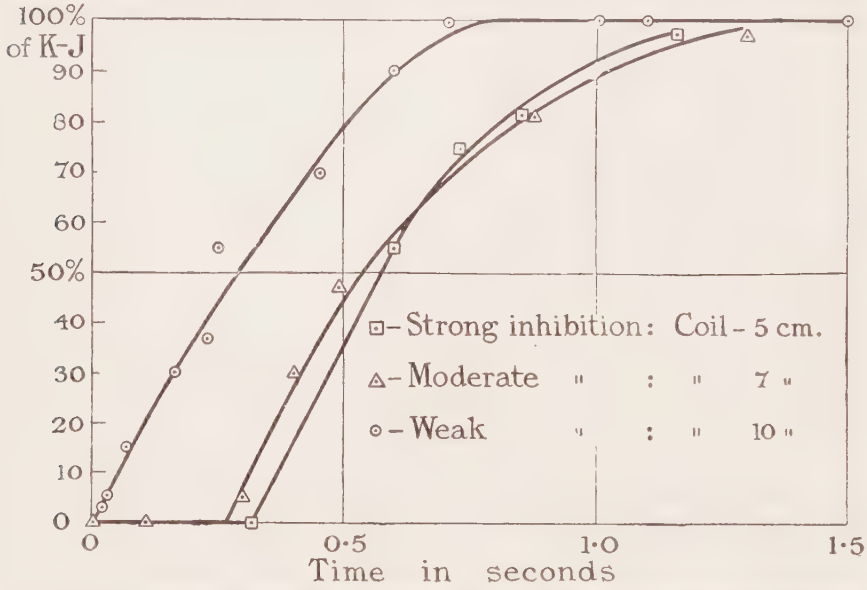

FIG. 125. Recovery curve of the knee-jerk of a spinal animal after a single inhibitory break-shock applied to the ipsilateral sciatic nerve. Ordinates = height of response expressed as percentage height (*i.e.*, tension) of a "normal" response to a series of equal taps. Abscissae = time in seconds after inhibition. The first curve (circles) shows the recovery from a "weak" inhibition (*i.e.*, coil 10 cm.); at this strength only when the tap and the inhibition were simultaneous was inhibition complete. The second curve (triangles) shows a stronger inhibition (coil 7 cm.), after which inhibition was "complete" for 0.3 second. A stronger inhibition (coil 5 cm.) is shown in the third curve (squares), but as recovery follows almost the same curve as the previous one, this suggests that the previous strength of stimulation was *maximal*. All responses shown in this graph were obtained from the same preparation within a period of thirty minutes. (*48*)

Other things being equal, the greater the strength of the inhibitory break shock, the longer the period of complete inhibition. Now it is evident that a period of complete inhibition must be due to suppression of activity of *all* the motoneurones involved in the knee-jerk. By suitably adjusting the strength of stimulation, an inhibitory effect may result which is complete only when the knee-jerk and the inhibitory stimulus fall simultaneously,

i.e., the period of recovery under these circumstances commences immediately after the inhibitory stimulus is delivered: the recovery curve, when plotted against time, crosses the origin (fig. 125, circles). The period of recovery gives evidence of a condition in which successive motoneurones recover one after another from the inhibitory stimulation.

When using single break-shocks for inhibition,—whatever their intensity might be,—no clear evidence was found of a period during which the jerks were supernormal in size following the period of recovery. This period, however, as Sherrington has originally pointed out, was clearly present when tetanic stimulation was used.

These observations admit of certain inferences concerning the duration of the period of after-discharge of inhibition in the spinal condition. When applied to the peripheral cut end of a *motor* nerve (*e.g.*, the anterior crural),

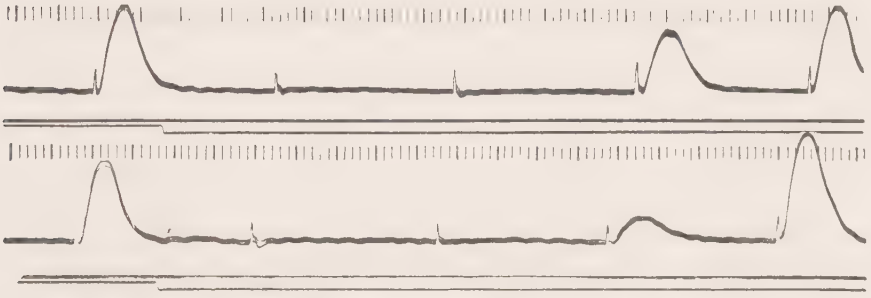

FIG. 126. Spinal preparation showing complete inhibition of the knee-jerk for a period of 1 second produced by a single stimulus. In the lower record the taps are smaller than in the upper. Strength of inhibition 8 cm. Time above = 0.02 second. String record not shown (see fig. 127). (*48*)

the strongest (single) stimuli used to produce these inhibitions, though well above the maximal value, were never found to be "supramaximal" in the sense of setting up two successive discharges (*321*). It is therefore justifiable to infer that they similarly did not set up repetitive discharges when applied to an afferent nerve, and this is supported also by the fact that in many cases a definite maximal strength of afferent stimulation was noted. For example, when the secondary of the Berne coil was moved down to 6 or 7 cm. the duration of the period of complete inhibition appeared to be no greater than when the coil was at zero. With less intense stimuli, *i. e.*, below 6 or 7 cm., however, the duration of the period of complete inhibition diminished progressively as the stimulus was made weaker and weaker.

When a "maximal" inhibitory stimulus was employed the longest period of *complete* inhibition observed was of 6 successive knee-jerks, *i.e.*, the

period lasted 2 seconds. In the majority of preparations, however, with maximal stimuli the period of complete inhibition did not last much more than 1 second (see fig. 126). The period of *complete* inhibitory after-discharge in response to a maximal stimulus lasts therefore in all motoneurones concerned for a corresponding period, *i.e.*, 1 to 2 seconds. However, *some* motoneurones are inhibited for a much longer period, that is to say, during the period of complete inhibition plus the period of recovery, and this may be as long as 3 or 4 seconds. It follows that the stronger inhibitory stimulus, *i.e.*, the greater the number of afferent fibres stimulated, the longer is the inhibitory after-discharge. This spatially additive feature of inhibition is precisely similar to the behaviour of the after-discharge of excitatory reflexes.

We have noted in a previous chapter that the first knee-jerks to emerge from inhibition of the spinal knee-jerk have the same duration as a motor twitch (fig. 128). The first motoneurones to recover from inhibition, in other words, are able to respond only once. When under weak inhibition, the spinal jerk is therefore indistinguishable from the decerebrate knee-jerk.

The decerebrate knee-jerk. When a series of knee-jerks of a *decerebrate* preparation is elicited in a similar way and inhibitory break shocks are applied as with the spinal jerks, the threshold for inhibition is much higher and the duration of the inhibitory effect more transient than in the spinal condition (fig. 127, cf. fig. 128). An inhibitory stimulus is most effectual when it occurs simultaneously with the tap on the tendon. In several instances, effective inhibitions were observed in which the inhibitory stimu-

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FIG. 127. Simultaneous electrical and mechanical records of knee-jerks of a decerebrate preparation elicited by successive finger taps. The taps are to be seen in the myographic record as initial upstrokes preceding the response. An inhibitory break-shock is applied to the ipsilateral (hamstring) nerve at the point indicated by the lower signal (one-half the distance across the plate). Line of zero tension above signal, and above that the galvanometer string: duration of mechanical responses about 65σ. Time at top of records = 0.02 second. Tendon movement magnified × 84 (in all figures).

A. Interval between inhibition and tap 0.10 second. Effect of inhibition very slight; note "tonic" after-discharge ("hump") towards the end of relaxation in each response. Coil distance = 13 cm.

B. Interval between inhibition and ensuing tap = 0.14 second. No effect on response, but note the decrease in "tonus" resulting from inhibition. Coil distance 0.

C. Interval between tap and inhibiton 14σ. Inhibition of jerk complete. Coil distance = 0.

D. Inhibition occurs 40σ after tap. Note inhibition of myotatic appendage ("hump"), as evidenced by comparing the first response with the second. Taps smaller in this record than in the preceding. (*48*)

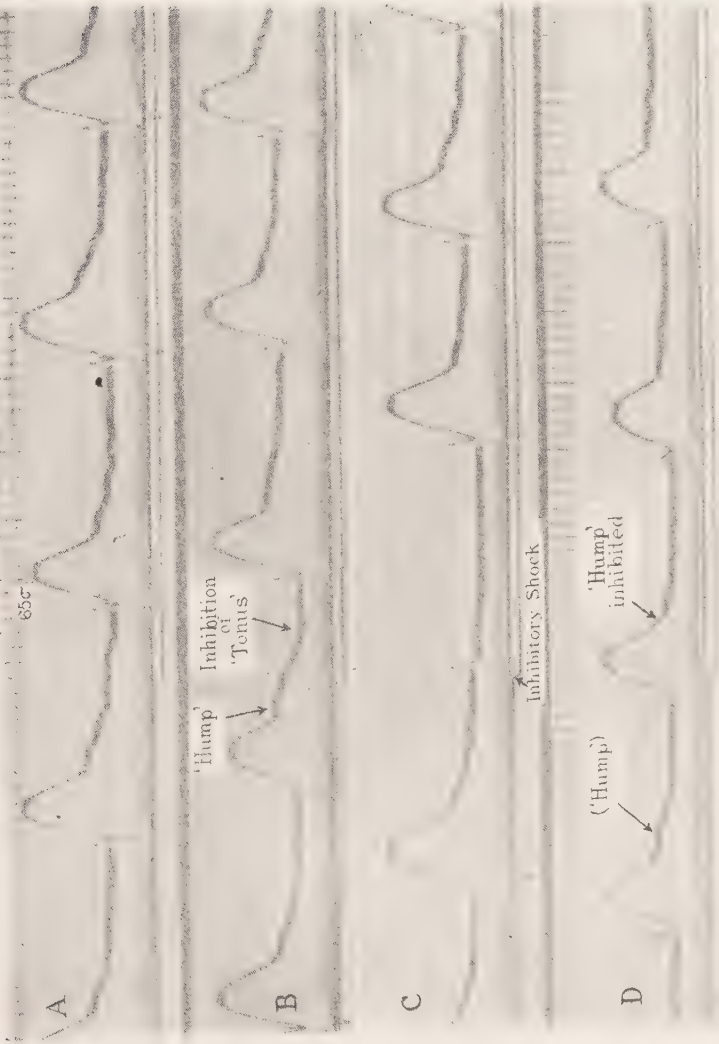
A
B
C
D
65°
'Hump'
Inhibition of 'Tonus'
Inhibitory Shock
('Hump')
'Hump' inhibited

FIG. 127

lus fell several sigmata *after* the tap. The inhibition was complete and this would appear to indicate that the latency of the inhibitory effect is even briefer than that of the knee-jerk itself (fig. 108 B).

It might be urged that part of the time consumed in the case of the knee-jerk is to be accounted for by the latency of the afferent endings. But Jolly (*524*) has shown this to be of the order of 0.4 to 0.5σ. Moreover, the average conducting distance for the afferent "stretch" impulses was, in these experiments, approximately equal to that of the inhibitory impulses; if anything, the distance from the cord of the latter was greater, since the stimuli were applied to the peroneo-popliteal trunk just above the knee-joint. Extensive delay in the passage of impulses through the posterior root ganglia can be excluded, for Erlanger, Bishop and Gasser (*286*), by means of the cathode ray oscillograph, find an interval of only $\pm 0.1\sigma$ not attributable to nerve trunk conduction time. Consequently, unless the conducting rates in these two functionally different groups of afferent nerves differ by a large percentage,—which, though not impossible, is nevertheless unlikely,—we are justified in concluding that inhibitory reflexes have a latency in the spinal cord even briefer than the knee-jerk.

This raises the question of the so-called "synaptic delay" in the spinal cord. It is probably true that in general reflex arcs which involve many synaptic junctions have longer reaction-times ("latencies") than reflex arcs with less extensive junctional connections, and that, therefore, the knee-jerk, since its latency is brief, has a correspondingly simple reflex arc. But to attempt to infer the *number* of synapses traversed from a finite time interval (*e.g.*, 2σ, Jolly's "reduced reflex time," *523*) is pure speculation. As we shall presently see, there is reason to believe that inhibitory arcs commonly involve an internuncial neurone in the cord, and yet the latency of inhibitory effect is *less* than that of so brief a reflex as that of the knee-jerk, which Jolly (*523*) believed to involve only one spinal synapse (see also *525*).

This harmonizes with the view put forward by Liddell and Sherrington that the locus of inhibition is far "down-stream" in the reflex arc, and suggests that it is in "final" motor neurones immediately supplying the fibres of the quadriceps muscle. Otherwise, it would be difficult to understand

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FIG. 128. "Spinal" knee-jerks of the same preparation as shown in figure 127 taken an hour later after section of spinal cord. Duration of "normal" mechanical response 90 to 100σ. Strength of inhibition = 13 cm. coil distance in all responses (applied to hamstring nerve). Other conditions as in figure 127. String tension 7 mm. per millivolt.

A. Two normal responses (first one partly cut off) followed by single inhibition. The duration of the first response emerging from the inhibition is 40σ, or approximately that of a (single volley) motor twitch.

The duration of the second response is longer (53σ), which suggests beginning of repetitive "firing." Note also the diminution in the electrical responses.

B. Same with complete inhibition of first response and 60 per cent recovery of second occurring 630σ after inhibition. Compare the electrical responses and note latencies.

C. Same with inhibition occurring 30σ after the tap.

D. Same showing *pari passu* recovery of three successive jerks. Slower plate. There is in this record a small ipsilateral reflex twitch caused by the inhibitory stimulus. (*48*)

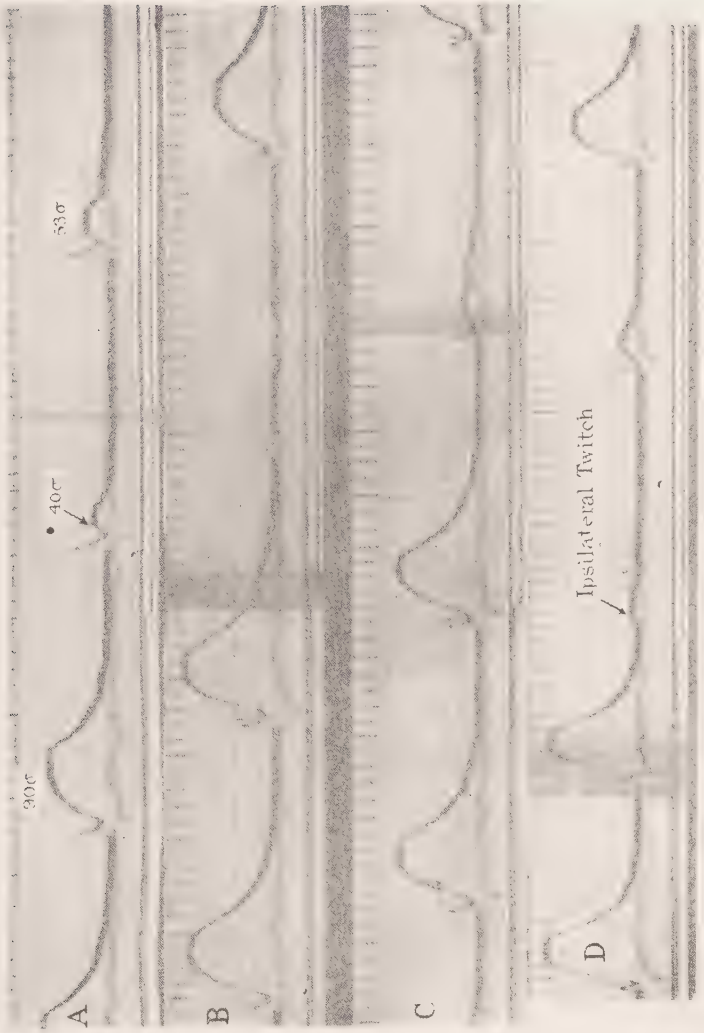

FIG. 128

how an inhibition falling at brief intervals *after* an excitation could inhibit that self-same excitation.

The period of complete inhibition of the decerebrate knee-jerk has, in our experience, not usually been greater than 0.10 second and ordinarily is considerably less. It has also been impossible to plot the curve of recovery, as it appears to occur with approximate simultaneity in all the motoneurones. In one or two instances sub-normal decerebrate knee-jerks were recorded at an interval of 80 to 100σ after the inhibitory stimulus, but we were never able to obtain a progressive series of such sub-normal responses. In view of the long period of inhibitory after-discharge and recovery observed in the spinal knee-jerk, the intervals which were observed in the decerebrate condition were notably short, and appear to indicate a fundamentally different condition of the motoneurones and of the inhibitory paths in the decerebrate state.

In a few preparations in which a high degree of decerebrate rigidity was present, it was observed that while the amplitude of the first jerk occurring after the inhibition was not reduced, that of the second and third jerks was considerably diminished (fig. 109, Chapter XI). Inasmuch as the stimuli used for these inhibitions visibly affected the fore limbs of the preparation, it appeared likely that the greater effect on the second knee-jerk is explicable on the assumption that the inhibition of the later jerks occurred indirectly through the mid-brain. Moreover these partially inhibited second and third jerks were curiously enough "spinal" in character, *i.e.*, of longer duration than ordinary decerebrate jerks. This suggests a temporary inhibition of the controlling higher centres, making the preparation for the time functionally spinal,—in short, an inhibition of an inhibitory influence. A consideration of the nature of the control exerted on the spinal centres by the higher centres of the nervous system will be deferred until a later chapter.

SPEED OF RELAXATION UNDER STRONG INHIBITION

When pitted against a crossed extensor reflex, a single strong break shock may, after a brief latency, lead to an abrupt relaxation the speed of which, as inferred from the photographic record, corresponds with the speed of cessation of activity of a motor nerve tetanus. The initial fall of the myograph, however, is not characterized by as sharp an "angle" as one observes in a motor nerve tetanus (fig. 129, also 124). The crossed extensor reflex is characterized preeminently by grossly asynchronous after-discharge. So marked indeed is this that the electrical responses are often scarcely observable (*319*, *364*). If, during a crossed-extensor reflex, the motor nerve supplying the muscle were instantaneously severed in such a way that no

additional impulses were set up by the section, the responses of the individually contracting units of the muscle would be in various stages of activity, depending upon the *rate of discharge* of the individual neuromuscular units. If one assumes an average rate of 200 per second (see Chapter XI) no individual response could have progressed for longer than 5σ. The commencement of relaxation under these circumstances would be an asynchronous composite, beginning 5σ sooner than the average duration of the individual responses. It is known from analysis of direct motor nerve responses that the duration of the single response during a tetanus plateau is somewhat less owing to shortening of the individual fibres than the duration of a twitch. A twitch response of 40σ would be associated with a response during the tetanus plateau of not more than 30σ in duration (*353*). It is

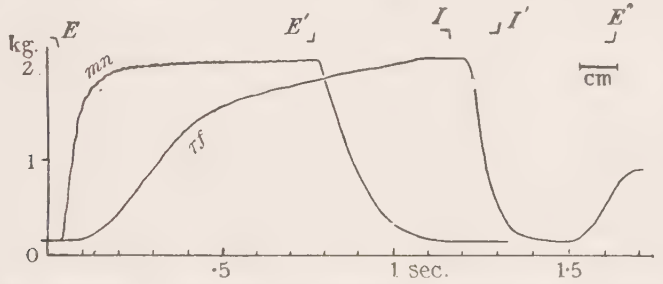

FIG. 129. *Quadriceps*. Relaxation from inhibition of reflex tetanus, *rf*, and from motor-nerve tetanus, *mn*, compared in the same preparation. Break-shocks at 50 per second used for both; at 16 cm. coil distance for former, at 26.5 cm. for latter. Inhibitory stimulus double shocks at 95 per second at 16 cm. coil distance. E to E′ excitatory stimulus for mn. tetanus; E to E″ excitatory stimulus reflex. I to I′ inhibitory stimulus. Tendon movement multiplied 35 times. Time in tenths second. (Liddell and Sherrington, *Proc. Roy. Soc.*, vol. 97B, p. 489, 1925.)

safe, therefore, to infer that the responses of the individual units during the tetanus plateau would be about 30σ in duration. If now the flow of impulses be abruptly cut off (as by inhibition) in a response in which none of the individual units have progressed more than 5σ in their response, the myograph will not commence to fall until 25σ have elapsed (30 minus 5).

It is therefore a point of considerable importance that the latent interval which Liddell and Sherrington (*641*) have observed between the delivery of the stimulus to the inhibitory afferent nerve and the onset of inhibitory relaxation is usually between 20 and 30σ, and they have met with latencies even as brief as 20σ. Possibly when as short a latency as 20σ is met with some individual units were discharging at a lower rate than 200 per second. In view of the fact that the conduction time of the afferent inhibitory volleys

of impulses, together with any possible time lost in transmission through the structures in the cord, is not more than 3σ (*v. supra*, Chapter XI), this observation makes it evident that an inhibitory stimulus is capable of arresting with approximate simultaneity the activity of the whole group of motoneurones involved in the reflex.

When the *rate* of "inhibitory" relaxation was compared with the rate of fall of a motor nerve tetanus, it was found that in the same experiment the rate was *actually somewhat greater* in the motor nerve relaxation than in the inhibitory, but this was found to be due to the fact of progressive slight deterioration of the preparation,—for the motor nerve responses were usually taken in any given experiment subsequent to the reflex responses (fig. 129). When, however, the motor nerve responses were recorded at the beginning of the responses, the rate of relaxation of the two was, within the limits of measurement and experimental error, identical (see table, p. 490 of Liddell and Sherrington's paper, *641*). It is evident that under these circumstances the excitatory activity of the motoneurones is extinguished with approximate simultaneity throughout the total aggregate of discharging units. In view of the fact that the motoneurone aggregate for quadriceps comprises at least 2000 motoneurones, this observation is of importance and the completeness and extreme brevity of the inhibitory latency is noteworthy.

THE INFLUENCE OF INHIBITORY STIMULI APPLIED AT VARIOUS POINTS IN THE COURSE OF A CROSSED EXTENSION REFLEX

"Stimulation," and "after-discharge" plateaus. We have seen that a single inhibitory break shock applied in the plateau of a crossed extensor reflex may cause sudden and complete relaxation of the response, but the ease with which such inhibition is brought about,—that is the strength of inhibition necessary for producing it,—varies at different points along the course of the reflex plateau. It is evident that the plateau of a crossed extension reflex is divisible into two parts: (1) The "stimulation plateau," that is, the first portion during which the excitatory stimuli are applied, and (2) the "after-discharge" plateau, or that during which the tension of the response is supported by the intrinsic activity (after-discharge) of the central mechanism. This second period commences at the end of an interval after the cessation of the excitatory stimulus equivalent to the latent period of the reflex. Occasionally when the rate of stimulation is visible in the mechanical record there is visible distinction between the two periods of the plateau, the "stimulation plateau" being characterized by small undulations corresponding to the rate of stimulation, while in the after-discharge plateau these undulations are absent.

From the standpoint of an inhibitory stimulus there is a great difference between the "stimulation plateau" and the "after-discharge plateau." An inhibitory stimulus of moderate intensity applied to the ipsilateral afferent nerve may provoke during the "stimulation plateau" only a slight notch in the course of the record. When a stimulus of the same strength is applied during the "after-discharge plateau," it may cause sudden and complete cessation of all activity. In other words, a break shock, to be adequate for suppressing activity in the face of concurrent stimulation, must

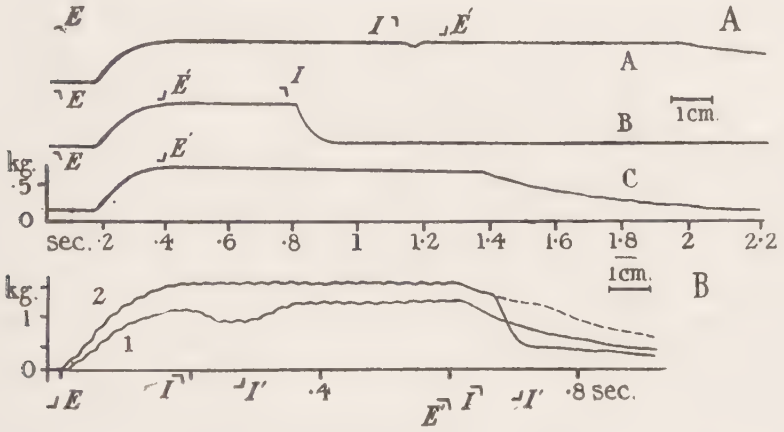

FIG. 130. A. *Vasto-crureus.* Inhibitory distinction between "stimulation plateau" and "after-discharge plateau" of reflex contraction. E to E′ stimulus of excitatory afferent at 39 break-shocks per second and 14.5 cm. coil distance. I, delivery of single break-shock to inhibitory afferent, at 12 cm. coil distance. A, delivery of inhibition in "stimulation plateau;" B, delivery in "after-discharge" plateau; C, repetition of reflex B with no inhibitory shock delivered. Tendon movement multiplied 45 times. Time in fifths second.

B. *Semitendinosus*, a flexor; decerebrate preparation; see text. The broken line gives the course pursued by the after-contraction in the control (uninhibited) reflex for reflex B. (Liddell and Sherrington, *Proc. Roy. Soc.*, vol. 97B, p. 493, 1925.)

be of very much greater intensity than that necessary to abolish after-discharge. This is shown in figure 130. These observations hold also of the ipsilateral flexor reflex of a decerebrate preparation which, as is well known, may be inhibited by a contralateral stimulation (Sherrington and Sowton, *043*).

Liddell and Sherrington (*641*) have concluded from these observations that the motoneurones discharging in the "after-discharge plateau" are the same both individually and in the aggregate as those discharging in the

"stimulation plateau," and it follows from their conclusions that an inhibitory stimulus "*finds one and the same motoneurone aggregate more difficult to arrest discharge in at one time than at another*" (p. 495). *In other words, a given motoneurone is more difficult to inhibit with a stimulus of given intensity at one moment than at another.*

Since this conclusion is of great importance to an understanding of the inhibitory mechanism, the possible objections to it may be considered. We shall see that in the stretch reflex the individual motor units appear to respond in rotation, and in this way long-sustained contractions are apparently capable of being maintained without fatigue. It may be urged similarly that during the plateau of a crossed extensor reflex a like rotation of activity also occurs, in which case the conclusion that the same motoneurone responding in the "stimulation plateau" also responds in the "after-discharge plateau" would not necessarily be valid. There are two reasons for believing that rotation of elements does not occur during the crossed extension reflex, or if it does occur that it is responsible for only a small fraction of the total tension maintained during the plateau: (1) In the case of the rotational activity observed in the stretch reflex the cause of the rotation is assigned to *rotation of activity among the afferent end-organs in the muscle.* The cause of rotation in this case is in the *method of stimulation* and not in the central activity. In the crossed extension reflex, on the other hand, the same group of afferent fibres engaged at the beginning of the response continue unchanged throughout the whole course of the reflex. There is, in other words, no rotation of activity among the *afferent* fibres, and it is unlikely, though unproved, that there occurs rotation of activity among the reflexly responding constituents. (2) One may also justify the inference on the grounds of the large number of reflex phenomena explicable on the basis of it, for it is not clear that any other assumption is consistent with as many observed facts.

The conclusion of Liddell and Sherrington, therefore, admits of certain inferences. The force which causes the individual motoneurones involved in the reflex to respond repetitively may be compared to a constant charge. Since the only way in which this constant force can find outward expression is through the all-or-none nerve impulses, its manifestation is a series of discontinuous impulses. The extent of after-discharge, therefore, may be taken as a measure of the "size" of the excitatory "charge" existing in individual motoneurone; the size may also be measured by the ease with which it may be inhibited, that is to say, by stimulus intensity. In the early part of the stimulation plateau an inhibitory stimulus of given strength is less effective than in a later part, and in the "after-discharge plateau"

it is very much more effective than in any part of the "stimulation plateau." The charge, or the amount of excitatory substance ("E-substance"), as Sherrington has called it (see the following chapter), in any given motoneurone tends to diminish progressively during the stimulation plateau and diminishes very rapidly during the after-discharge plateau. Since nothing comparable to after-discharge occurs when the axon of the motoneurone is stimulated the accumulation of these substances must therefore lie central to the axon of the motoneurone. It follows from this that the way in which a reflex employs its motor unit is to subject them to a form of excitation which is supramaximal in the sense that it may be much in excess of that which is necessary to evoke in them individually a maximal response. The places in which such supramaximal accumulations of excitatory substance are confined must be limited to the aggregate of motor units involved in the particular reflex excited, otherwise there would be spreading of reflex activity and the grading of intensity of contraction would be obliterated. To visualize these loci of concentration as discreet histological units such as the nerve cell bodies or (less likely) the synapses is, as Liddell and Sherrington have pointed out (p. 497), in accord with the structure of the grey matter of the nervous system.

Repetitive discharge recurring in individual cells in response to a single stimulus recalls physiology of the rods and cones in the eye. It is known that a light stimulus of several millionths of a second duration will, if sufficiently intense, set up a visual image producing in its train after-images of many seconds duration. The after-images, according to present physiological conceptions, are due to the repetitive activity of the individual retinal elements, and in this way are closely comparable to the repetition which occurs in the motoneurone. One would picture a chemical change set up, in the case of the units in the eye, by radiant energy, in the case of the anterior horn cells by impinging nerve impulses. In both cases the exciting agent thus liberated leads to a reaction at some cellular interface, possibly at the axon-hillock, and in this way gives rise to a series of nerve impulses which continue until the concentration of the excitatory substances has fallen below the threshold value.

EFFECTS PRODUCED BY VARYING THE INTENSITY AND DURATION OF INHIBITORY STIMULI

Inhibitory recruitment. When an inhibitory stimulus, repetitive in character and of weak intensity, is applied during the stimulation plateau of a crossed extensor reflex, *e.g.*, at 36 per second (see figs. 131 and 132) the

subsidence of active tension in the musle occurs gradually and ultimately attains completeness. The strength of stimulation can be so chosen that the time required for such a relaxation to complete itself may be a second or

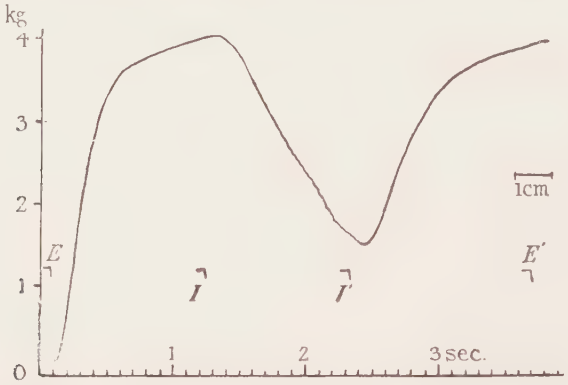

FIG. 131. *Quadriceps extensor.* E to E′ stimulus of excitatory afferent by double shocks at 95 per second and 15.5 cm. coil distance; I to I′ stimulus of inhibitory afferent by break-shocks at 35 per second and 14.5 cm. coil distance. Tendon movement multiplied 67 times. Time in tenths second. (Liddell and Sherrington, *Proc. Roy. Soc.*, vol. 97B, p. 497, 1925.)

FIG. 132. As in figure 131, but inhibitory stimulus at 15.7 cm. coil distance. (Liddell and Sherrington, *Proc. Roy. Soc.*, vol. 97B, p. 499, 1925.)

more and the shape of the curve may be almost rectilinear. Inhibitory relaxations under these circumstances run a very different course from the decline of tension of a motor nerve tetanus. It is clear that inhibition of this character does *not* abolish motor discharge simultaneously in the

total group of motoneurones which it attacks. With mere continuance of an unaltered inhibitory stimulus a progressive decrease in tension occurs, which appears to be similar in every way, but in reverse direction, to the recruitment process described in Chapter XII. The "derecruitment" or *inhibitory recruitment*, as it has been called, has many points in common with the reverse process, and the balance of evidence indicates that it is similarly caused; that is, under continuance of the inhibitory stimulus of

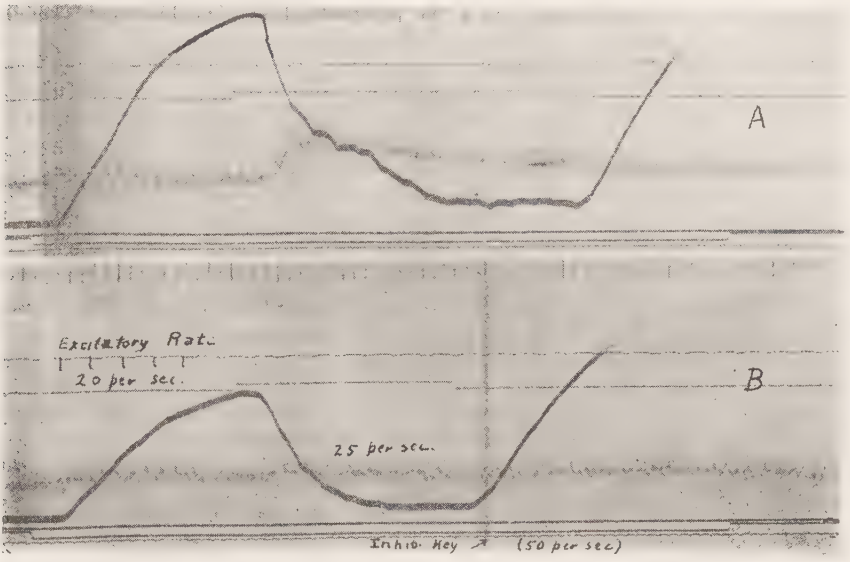

FIG. 133. Two records obtained by Liddell and the author of the inhibition of a crossed reflex quadriceps extensor of a decerebrate cat, showing "primary" excitatory rhythm of 20 per second, and during inhibition a sub-multiple of the inhibitory rate (50 per second) of stimulation. The larger waves during the inhibition are at 25 per second, and in the upper record large waves occur at $12\frac{1}{2}$ per second, alternating with small ones at that rate.

unaltered intensity, progressively large numbers of active motoneurones are one by one suppressed.

Inhibitory rhythm. Prominent among the features of inhibitory recruitment is *rhythm* in the mechanical record. This rhythm may be either that of the excitatory rate of stimulation, or of the inhibitory rate, or some sub-multiple of either one (*364*). The circumstances under which one or the other of these rhythmns occur have not been completely elucidated, but the facts which have been established are as follows: (1) When occurring during stimulation plateau, *weak* repetitive inhibitory stimuli or a single *strong* inhibitory stimulus causes the appearance in the mechanical record (and electrical record; fig. 174)

of the *excitatory* rhythm, usually in its full rate. "The partial inhibition dissects out, so to say, the ribs of reflex contraction, so that against the ill-supported remainder they [the excitatory "ribs"] become prominent like the ribs of an ill-nourished child" (*641*, p. 500). (2) When an inhibitory stimulus, slow in rate, and not of sufficient strength to abolish contraction instantaneously occurs during a given reflex "stimulation plateau" elicited by a *high* rate of excitatory stimulation, the inhibitory rhythm, or some sub-multiple of it, generally occurs in the mechanical record. (3) Finally, a repetitive inhibitory stimulus occurring during after-discharge produces a step-relaxation provided it is of moderate intensity, and the steps correspond to the rate of inhibitory stimulation.

To account for these observations one may take the case (fig. 174) of a single strong inhibitory stimulus occurring during a stimulation plateau of a reflex. The smothering of excitatory rhythm in the crossed extension reflex is due to after-discharge (*637*, *364*; see Chapter XII); therefore, any factor tending to diminish after-discharge will tend also to render visible the rhythm of excitatory stimulation. This is precisely what a single inhibitory impulse does, provided it is not so strong as to abolish all activity. Similarly, a weak repetitive stimulus occurring during a stimulation plateau will attack the after-discharge rather than the volleys of impulses set up directly by the excitatory stimuli. When a stronger repetitive inhibition occurs, especially when the rate of stimulation is greater than that of the excitatory rate, both rhythms sometimes appear in electrical and mechanical records and the predominant rhythm will be determined by whichever of the two is relatively the stronger. When occurring during the "after-discharge plateau," in which excitatory repetition occurs asynchronously among individual units and at a high rate, groups of neurones will,—owing to inhibitory recruitment,—tend to be suppressed at regular time intervals corresponding with the rate of inhibitory stimulation. Fulton and Liddell (*364*) have observed that *whenever a pronounced rhythm is to be observed in the myograph record there is always a corresponding rhythm in the action currents* (fig. 133). When an action current occurs in a muscle it means that a large number of the muscle units commence to contract with approximate simultaneity. By inference, therefore, rhythm in a mechanical record gives evidence of the same fact. It is simple to account for an excitatory rhythm giving rise to action currents of corresponding rate, but more difficult to provide an adequate explanation for the action currents which occur at an inhibitory rate. Mere cessation of activity, though occurring synchronously, would not give rise to an action current, especially when, previous to cessation, the groups of fibres were responding out of phase. Fulton and Liddell have concluded that such inhibitory rhythms, when they occur in the string, are caused, in part at least, by small uninhibitable groups of muscle fibres in quadriceps which respond to ipsilateral stimulation by contraction. Following inhibition, as already mentioned, they found that when inhibition was complete, that is, during the post-inhibitory notch and during the fall of the myograph leading to the formation of the post-inhibitory notch, the galvanometer string is absolutely quiet.

The tendency of excitatory and inhibitory rhythms to become halved or to become reduced into some other sub-multiple of the original rhythm is difficult to explain except by temporal summation. It would appear in the case of a halved excitatory rhythm that only every second stimulus "gets through" to the motor centre, and probably the same is true of the corresponding phenomena in inhibitory rhythms. The formation of sub-multiples in the case of inhibitory rhythm is also very commonly observed (see fig. 133). The explanation of the formation of sub-multiples of stimulation rhythm has many points in common with Lewis's (*629*) explanation of "alternation" in the case of heart

muscle. It is interesting in this connection that Pratt (*781*, p. 536; see his figure 5) obtained a similar alternating rhythm when stimulating a single fibre tetanically at an intensity near the threshold. The fibre responded regularly to every fourth (? fifth) stimulus. Presumably when the intensity of stimulation is in the just effective region the threshold of the fibre fluctuates, owing to activity, and "alternation" results.

von Brücke (*171*) has observed the formation of sub-multiples of excitatory rhythm in response to stimulation of the posterior roots of the frog.

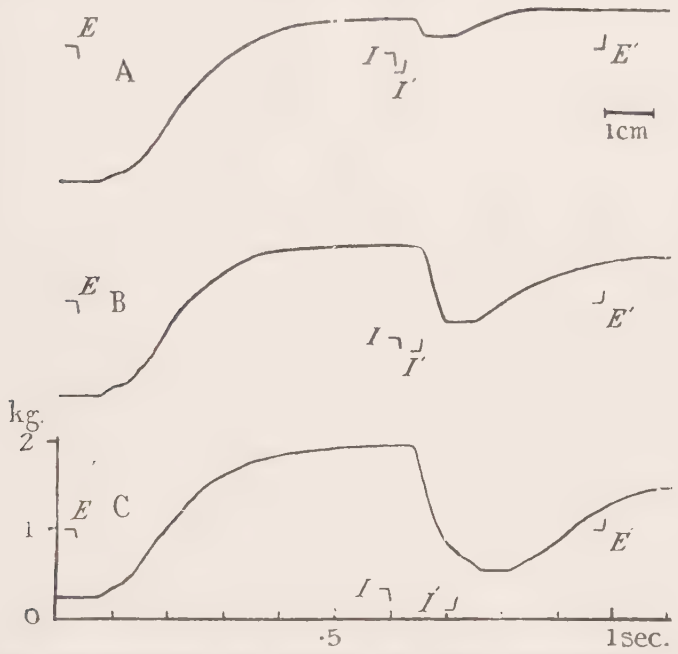

FIG. 134. *Rectus femoris* and part of *crureus*. E to E′ stimulation of excitatory afferent by magneto at 46 per second and 11 cm. coil distance. I to I′ stimulation of inhibitory afferent by double shocks at 95 per second and 16.5 cm. coil distance. Duration of tetanic stimulation of inhibitory afferent longer in B than in A, in C than in B. Tendon movement multiplied 50 times. Time in tenths second. (Liddell and Sherrington, *Proc. Roy. Soc.*, vol. 97B, p. 506, 1925.)

Comparison of inhibitory and excitatory recruitment. Inhibitory and excitatory recruitment have the following features in common. The process occurs more rapidly, (1) when the stimulus frequency is increased (within limits), (2) when the stimulus intensity is increased, (3) in the corresponding durations of the period of ascent (excitatory recruitment), on the one hand, and the periods of descent (inhibitory recruitment) on the other, the two processes are strikingly alike, (4) if one makes allowance for the latent period

of the reflexes, the time interval after cessation of stimulus after which recruitment ceases, is the same for both excitatory and inhibitory phase of activity, (5) another point in common between the two processes comes from a comparison of what may be termed the kinetic and static phases of their respective activities. As shown in figure 134, when an inhibitory stimulus of constant intensity but varying duration (*i.e.*, number of repetitions) occurs at the same point in consecutive crossed reflexes of the same amplitude, the inhibitory notch so produced in the record varies in depth with the duration of inhibitory stimulus, and the downstroke,—which may be termed the "kinetic" phase of the inhibition,—corresponds closely in duration with the duration of the stimuli. However, the downstroke stops abruptly and for a brief period there follows a horizontal plateau in which the contraction remains at the level reached by it at the end of the relaxation descent. With the strength of stimulation employed in figure 134, this flat region of the record lasts 50σ. Such a flat plateau does not occur in the record of motor nerve responses when several stimuli are allowed to lapse during the tetanus plateau, though the downstroke of the relaxation ensuent upon lapsing of stimuli from the motor nerve plateau is in every way similar to the kinetic phase of such an inhibition. From the standpoint of recruitment, this brief flat plateau,—the static period of inhibition,—clearly represents an interval during which recruitment of added motoneurones is prevented. This is also borne out by experiments in which similar inhibitory stimuli are applied during the ascent of the crossed extensor reflex record. The response to such stimulation, when not too strong or of too great duration, is a check in the ascent similar in every way to the check in the ascent described above, which resulted from lapsing of excitatory stimuli during that period. This inhibitory "deviation of the contraction ascent" is thus also attributable to the prevention of recruitment of added motoneurones by the excitatory stimulus.

The short plateau ensuent upon the descent of such inhibitory notches reveals what may be termed the after-discharge period of inhibitory effect. Such inhibitory notches, as shown in figure 134, can also be obtained in varying depths by mere increase of intensity of a single break shock stimulus, and with increasing strengths of stimuli the inhibitory after-discharge shows itself for longer periods.

A question therefore arises as to the relation between inhibitory after-discharge, as documented by the flat plateau of such records as that shown in figure 134, and the after-discharge of inhibition determined by means of the knee-jerk. We have seen, in the case of the decerebrate knee-jerk, that the period of complete inhibition of all motoneurones involved may con-

tinue for about a tenth of a second, and a period of partial inhibition, that is, one in which not all of the neurones are suppresssed may continue for another tenth of a second. The duration of inhibitory plateau is of this order of magnitude, but is usually somewhat less. It must be remembered, however, that the inhibition, in the case of contralateral reflexes, acts in the face of concomitant excitation, which therefore tends to reduce its effect, while with the knee-jerk the inhibitory after-discharge has little or no preexisting activity to counteract it. In the spinal knee-jerk, on the other hand, the duration of the period of inhibitory after-discharge is greatly lengthened and may be of the order of 2 seconds. Unfortunately no observations have as yet been made upon the inhibitory plateau in spinal reflexes.

Inhibition of after-discharge and the "eclipse." In a crossed extensor reflex a common feature of the relaxation evoked by a single inhibitory break-shock applied during the reflex stimulation plateau" is that there occurs an initial fall to a horizontal level which continues for a varying period depending upon the strength of the inhibition and the point at which it is applied during the plateau. The result is a two-stepped relaxation. The size of the initial descending step is greater (1) the more intense the inhibitory stimulus, (2) the later the inhibitory stimulus falls along the stimulation plateau. The myogram of such an inhibition thus indicates that part of the motoneurones involved in the reflex are thrown out of activity. The terminal portion of the relaxation (*i.e.*, the second step) shows that the remaining active neurones are practically unaffected by the stimulus. "In other words the inhibition, affecting as it does a certain proportion only of the motoneurones engaged in the reflex contraction, extinguishes the discharge in those only of them whose after-discharge would, were the reflex contraction allowed to pursue its course unmodified by inhibition, endure least long. That is, the inhibition quells more easily those motoneurones in which, quite apart from inhibition, discharging activity will, after withdrawal of the excitatory stimulus, lapse sooner than in the rest. Therefore, some same circumstance, which makes after-discharge in a motoneurone long-enduring, also fortifies a motoneurone against inhibition." (641, p. 510). Liddell and Sherrington point out that this observation lends support to the view that the central excitatory process finds outward expression in a mechanism whose response to excitation is all-or-none in character.

Another important feature of the inhibition of after-discharge is the so-called "eclipse."

Since inhibitory stimuli quell after-discharge and tend to prevent recruitment of added muscle units, it is of interest to examine the effect on the

duration of after-discharge of an inhibitory stimulus occurring either before a given reflex contraction, or very early in the reflex response. If an unmodified crossed extensor reflex, such as that shown in figure 135, is compared with a similar reflex in which an inhibitory stimulus was delivered immediately preceding the reflex or during the initial stages of the ascent it is found that the terminal after-discharge is very considerably abbreviated. This abbreviation of terminal after-discharge by a precurrent inhibition has for convenience been termed the "eclipse." It emphasizes the prolonged duration of inhibitory effect and also indicates that "the central inhibition's after-discharge conspires with the cause underlying spontaneous lapse of after-discharge to bring about an ante-dating of the cessation of the after-discharge." The extent of the eclipse appears to be determined by the

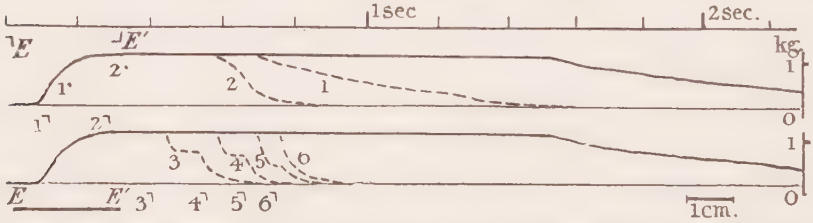

FIG. 135. *Vasto-crureus.* Instances of "eclipse" of after-discharge; E to E', excitatory stimulation break-shocks at 38 per second at 16.5 cm. coil for A, at 15.5 cm. for B; during B a single break-shock at 18 cm. coil to inhibitory afferent. In upper figure (1) the inhibitory stimulus is delivered at points within the period of the excitatory stimulation; in lower figure (2) the inhibitory stimulus is delivered at points within the after-discharge period of the excitatory reflex. Tendon movement multiplied 45 times. Time in tenths second. Explanation in text. (Liddell and Sherrington, *Proc. Roy. Soc.*, vol. 97B, p. 513, 1925.)

relative intensity of excitatory after-discharge and inhibitory after-discharge. When tested at various points along the contraction both of the stimulation plateau and the after-discharge plateau the eclipse becomes progressively increased in extent and modified in shape as the stimulus occurs later and later in the reflex. Records showing these features are reproduced in figure 135.

SUMMARY

In this chapter are recorded the more important experimental facts relating to the central inhibitory process. They are set forth to serve as a basis for analysis of the intimate mechanism of central inhibition elucidated in the following chapter. In simple spinal reflexes the locus of the inhibitory process may be as far "down-stream" in the reflex arc as the motoneurones

of the final common path. It is so situated as to enable inhibition of after-discharge of these neurones.

A single inhibitory break-shock applied to an ipsilateral afferent nerve may inhibit the spinal knee-jerk for a period of one to 4 seconds. Other things being equal, the higher the intensity of the inhibitory stimulus the longer the period of complete inhibition. Since the spinal knee-jerk is a short tetanus, an inhibitory stimulus applied within 10 to 15σ after the beginning of the knee-jerk diminishes its duration owing to inhibition of repetitive after-discharge. The inhibitory effect occurs within 3σ of the application of the stimulus, of which interval at least 1σ is consumed in conduction time.

The decerebrate knee-jerk is 10 to 20 times less susceptible to inhibition than is the spinal jerk; moreover, the condition of inhibition in the decerebrate animal continues for only 0.1 second after application of a strong ipsilateral stimulus.

The speed of relaxation of a crossed extensor reflex under strong inhibition approximates the rate of relaxation from a motor nerve tetanus.

A distinction is made between the so-called "stimulation plateau" and the "after-discharge" plateau of a crossed extensor reflex. Reasons are given for inferring that the same motoneurones are in activity during both portions of the reflex plateau. It is more difficult to inhibit a crossed extensor reflex during its "stimulation plateau" than during the "after-discharge" plateau; consequently, one and the same motoneurone is more difficult to inhibit at one time than at another.

The gradual relaxation which occurs on continuance of application of a weak inhibitory stimulus is designated "inhibitory recruitment," and it is shown to possess all of the characteristic features described in Chapter XII as typical of excitatory recruitment.

The significance of inhibitory and excitatory rhythms and of the tendency for the occurrence of sub-multiples of either one, both in the electrical and mechanical records of reflex responses, is decribed. The formation of sub-multiples has a counterpart in the phenomenon of "alternation" of heart muscle. A weak inhibitory stimulus "uncovers" a smothered excitatory rhythm, since it attacks the after-discharge of the excitatory stimulus more readily than the immediate excitatory response.

The phenomenon of the "eclipse" of after-discharge is described and its significance discussed.

CHAPTER XIV

The Nature of the Central Excitatory and Inhibitory Processes[1]

In any form of locomotor activity it is as important to be able to stop at a desired instant as it is to be able to start, and "desistance from action may be as truly active as the taking of action" (*925*, p. 251). In the evolution of the central nervous system the powers of inhibition have developed side by side with those of excitation, but while excitability has long been investigated, the study of the nature of inhibition is comparatively recent. It was initiated in 1846 by the discovery of the brothers Weber (*1034*) that stimulation of the peripheral end of the vagus nerve causes temporary cessation of the heart beat. So striking at first did this discovery seem that many hesitated to accept it. Eventually, however, it became generally recognized and the search for other inhibitory nerves soon began. Thirteen years later Pflüger (*771*) showed that intestinal movements could be inhibited by stimulation of the splanchnic nerve, and in the preceding year (1858) Claude Bernard (*86*, vol. ii, p. 144) discovered the action of the corda tympani, and found, among other things, that it inhibited the musculature of the submaxillary artery and its branches. The search was continued always with the expectation of finding inhibitory nerves to skeletal muscle. Hope was very often aroused, especially by Pavlov's (*761*) discovery of the inhibitory nerves passing to the adductor muscles of the bivalve, *Anodon*, and similarly by Biedermann (*102*), in finding the inhibitory nerves of the claw muscles of the crayfish, *Astacus*, but no one has ever discovered inhibitory nerves for vertebrate skeletal muscle.

Although, when completely separated from their connections with the neuraxis (*i.e.*, the whole central nervous system), vascular and visceral muscle still exhibit phasic activity involving both excitation and inhibition, skeletal muscle stands as a striking contrast to this independence of central control. Every contraction of a skeletal muscle results from a discharge of the central nervous system. After its nerve has been cut a muscle never contracts again, save it be artificially stimulated, or save its nerve be permitted the long and tedious process of regeneration. As Sherrington (*925*) has expressed it: "section of its nerve, even when the muscle

[1] The writer wishes to acknowledge his indebtedness to Dr. Hallowell Davis for extensive revision of this chapter.

remains *in situ*, causes it to lapse into a paralytic quietude so profound that its very structure becomes in a short time hardly recognizable as muscle" (p. 252).

It is this very dependence upon the neuraxis which has rendered unnecessary specialized inhibitory nerves for skeletal muscle, since mere cessation of nerve stimulation appears to be as effectual in arresting contraction as an "active" inhibitory process, such as that which occurs in the heart. An inhibitory control over the motor nerve centres of a muscle would therefore be as efficient as direct control over the muscle itself, and this indeed appears to be the way in which nature has solved the problem of inhibition of the skeletal musculature of higher animals (*922*). The behaviour of skeletal muscle may accordingly be regarded as a faithful index of the state of its motor centre. In studying the nature of the central inhibitory process therefore, our most satisfactory guide is the behaviour of the muscle itself, but any inferences which we draw have the disadvantage of being to this extent indirect.

Of the many theories of central inhibition which have been proposed, only two in recent years have had active protagonists. It is permissible therefore to pass over such hypotheses as the assimilation theory of Gaskell and Hering, McDougall's drainage or diversion theory, and several others which, owing to the lack of experimental evidence in their favour, are merely of historical interest. A discussion of them will be found in Bayliss's (*59*) suggestive chapter on excitation and inhibition, and in Howell's (*501*) recent review on inhibition. The two postulations, which recently have taken definite shape, may for brevity be termed the "interference" and the "chemical" theories. "Interference" is of course used in the somewhat specialized sense introduced by Wedensky (*1035*, *1036*), and it has no reference to von Cyon's old comparison of inhibition with such purely physical interference as occurs in light or sound waves. Howell (*501*) refers to the Wedensky interpretation somewhat more accurately as the "impairment and decrement" theory, though "decrement" *per se* is not indispensable to the hypothesis (*318*, *330*). The main support for the "interference" theory is derived from Lucas's (*663*, *664*, *665*) experiments (in peripheral nerve-muscle preparations) on the so-called phenomenon of Wedensky inhibition, and from Adrian's (*2*, *9*, *17*) and Forbes's (*318*) analysis of the central inhibitory process. According to the chemical view, inhibition is believed to be due to the formation of an "active" inhibitory substance somewhere in the path of conduction of the impulse. The main support for this theory comes on the one hand from investigations of the effect of drugs (and certain perfusates) on peripheral tissues, especially on the heart, and

on the other from Sherrington's (*922, 925, 936*) and Samojłoff's (see note, p. 363) studies of the central inhibitory process.

THE INTERFERENCE THEORY

The early observations on peripheral tissues which led to the promulgation of the interference theory are well known, and since they have been described at length in Keith Lucas's (*665*) monograph on the *Conduction of the Nervous Impulse* (Chapter XII), they need not detain us here. It is sufficient to say that Schiff (*852*) was the first to observe that when the peripheral nerve-muscle system is stimulated at a high frequency, contraction subsides after several initial responses, and that so long as the stimulation continues the muscle remains recalcitrant to super-added stimuli applied lower down on the nerve. Schiff's experiment was carried further in 1885 by Wedensky (*1035*), who found that nerve stimulation was necessary for the production of this variety of apparent inhibition, and that it would not occur in a curarized muscle stimulated directly (cf. Veach, *997*). Wedensky (*1036*) later found that if a short stretch of nerve were narcotized, the effect might be produced in the nerve trunk itself, for it was found that impulses of a high frequency do not pass the block, whereas single and slowly repeated stimuli do pass. The basis of this relative ineffectiveness of impulses of high frequency was made clear by Lucas (*663*). He showed that a stimulus applied to a nerve or muscle during the relative refractory period following a previous impulse gave rise to an impulse which was subnormal in magnitude. The subnormality was inferred both from a reduced electrical response, and from a diminished ability to pass through a region of impaired conduction or "decrement." The subnormal impulse also leaves the nerve in a refractory state, and a third impulse following closely enough behind it will also be subnormal, and will be extinguished like the second in a region of impaired conduction. According to Lucas, the region of impaired conduction at which the subnormal impulses are extinguished may be a neuromyal junction, particularly a "fatigued" one (cf. above, Chapter VI), or a narcotized region of nerve. It is important to recognize that the blocking of the second of two impulses separated by a very brief interval is an *empirical fact*, and does not depend on the theoretical interpretation in terms of decrement which Lucas offered. Therefore the work of Kato (*541*), showing the older theory of decremental conduction to be fallacious, does *not* affect the interference theory of inhibition. Moreover, Davis, Forbes, Brunswick, and Hopkins (*227, 228*), while confirming Kato in the main, have pointed out that his conclusions are not justified when applied to a *very short* region of depressed response. They

maintain on theoretical grounds, that conduction with a decrement must occur, representing a gradual transition between normal and subnormal response, and their considerations are certainly of importance for regions of the magnitude of synapses and neuromyal junctions. Perhaps the simplest and most satisfactory interpretation of the Wedensky effect at a neuromyal junction is that proposed by Forbes (*318, 330*), who pointed out that if we regard the nerve action current as the cause of excitation of the muscle fibre, it is not difficult to suppose that the threshold of excitation of

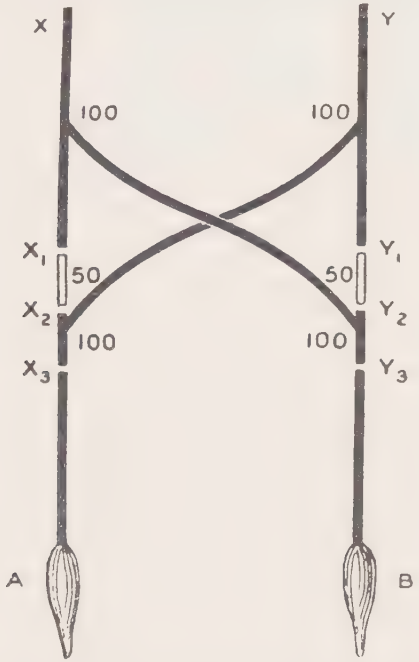

FIG. 136. Lucas' diagram (*665*) to account for reciprocal inhibition on the basis of the Wedensky hypothesis For description see quotation from Lucas.

the muscle might be such that a normal response of the nerve would serve to excite it, while a subnormal response would be inadequate.

For application of these conceptions to the theory of central inhibition, it is necessary to refer to the special schema originally suggested by Lucas (*665*) and since amplified by Adrian (*9, 14*) and Forbes (*318*). In figures 136 and 137, these schemata are reproduced. They are all adapted for explanation of the phenomenon of reciprocal innervation of antagonistic muscles. According to Lucas's original diagram (*665*), a series of stimuli

applied to an afferent nerve X (*e.g.*, right popliteal) causes contraction in the muscle A (*e.g.*, right semitendinosus, a flexor), and simultaneous inhibition of muscle B (*e.g.*, right vastocrureus, an extensor), while stimuli applied to the other nerve Y have precisely the opposite effect. In the words of the Lucas (*665*) monograph:

"Let us suppose that in the nerves X and Y recovery takes place at such a rate that 100 impulses can be conducted in one second without very much reduction in intensity. X is in communication with the muscle A by two relays X′X″ and X″X‴. Suppose the tract X′X″ to have a long refractory period so that every other impulse from X arrives at a time when X′X″ cannot conduct at all. The result will be that only 50 impulses a second will pass into X″X‴. Now the nerve Y has a branch passing directly to X″ without the intervention of the tract X′X″. Consequently Y will send 100 impulses to X″ whereas X sends only 50. The tract X″X‴ recovers at such a rate that if only 50 impulses reach it one second each impulse will fall in the phase of supernormal recovery,

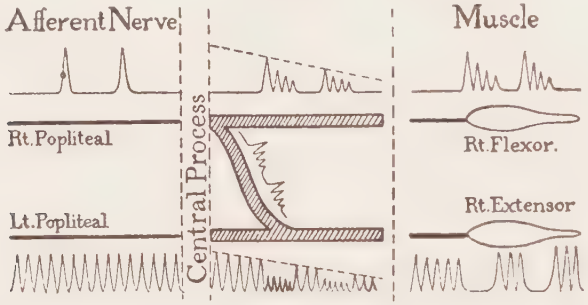

FIG. 137. One of Adrian's amplifications of the schema given in figure 136; it was designed to account for his observations on the electrical responses of flexors and extensors. (*Brain*, vol. 47, p. 413, 1924.)

and will be large enough to pass the junction at X‴ and reach the muscle A. On the other hand, if the impulses occur at a frequency of 100 a second each will fall in the phase of subnormal recovery, and none of them will be large enough to pass the junction at X. Thus the stimuli at X will give a contraction in A and the stimuli at Y will have no effect. Actually A is in a state of slight tonic contraction which we may suppose to be maintained by impulses arriving at X″ from some other part of the central nervous system. The impulses from Y will reduce these also and so there will be a relaxation of the muscle when Y is stimulated. The same arrangement in the case of the muscle B will lead to inhibition following stimulation of X and contraction following stimulation of Y."

Explanations along these lines have been discussed at some length by Forbes (*318*), Adrian (*9*), Cooper and Adrian (*14, 210*), Brücke (*171*), and Beritoff (*70a, 75, 70*). This theory has the advantage of explaining inhibition in terms of the known properties of nerve fibres, without invoking any assumption of properties and mechanisms in the central paths of conduction

different from those existing in the axons of nerve fibres and their junctions with effector organs (see fig. 138).

Within the last few years experimental evidence in favour of the interference theory has been sought in a number of different ways. Brücke (*171*), for instance, working with the crossed extensor reflex, employed the ingenious method of using simultaneously excitatory and inhibitory stimuli of slightly different frequencies, *e.g.*, 50 and 51 the second. At their commencement the two series coincide, but become progressively more out of phase with one another until they alternate at intervals of 0.01 second;

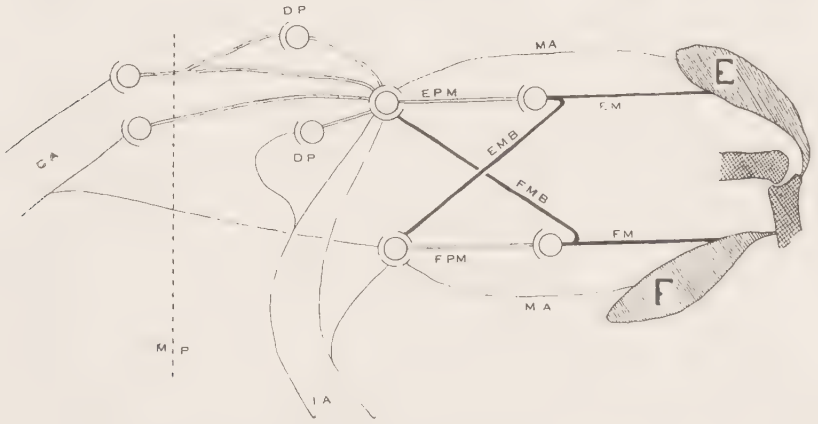

FIG. 138. Forbes' diagram of spinal neurones and their connections providing a possible basis for analysis of reflexes. Afferent neurones shown in light lines; internuncial neurones in double lines; motor neurones in heavy lines. *E*, extensor muscle; *F*, flexor muscle; *MP*, median plane; *CA*, contralateral afferent fibres; *IA*, ipsilateral afferent fibres; *DP*, delay paths, representing extensive central connections to provide for prolonged after-discharge; *EPM*, extensor pre-motor neurone; *FPM*, flexor pre-motor neurone; *EM*, extensor motor neurone; *FM*, flexor motor neurone; *EMB*, collateral branch of extensor motor neurone; *FMB*, collateral branch of flexor motor neurone. (*Physiol. Rev.*, vol. 2, p. 397, 1922.)

the difference of phase then becomes smaller until it once more becomes zero, the whole cycle having the duration of one second. When the intensities were so adjusted as to produce partial inhibition, contraction was observed to wax and wane rhythmically every second, the inhibition being greatest when the excitatory and inhibitory were in phase. The inference drawn from this is that the inhibitory effect must dwindle with great rapidity, for a change of 10σ in the time of incidence of inhibition is sufficient to render the inhibition less effective. Beritoff (*70a*) has provided similar evidence from a partially inhibited muscle. A flexor muscle was

made to contract reflexly at 200 per second (ipsilateral peroneal nerve), and action currents recurred in the muscle at that frequency; when partially inhibited by contralateral stimulation at 25 per second, the record showed gaps corresponding in rate to the inhibitory frequency. From an analysis of such records Beritoff (*70a*) came to believe that the inhibitory effect of each stimulus may be as brief as 4σ. These inferences are drawn entirely from string galvanometer records. When stronger stimuli are used the duration of each pause becomes longer until complete inhibition results.

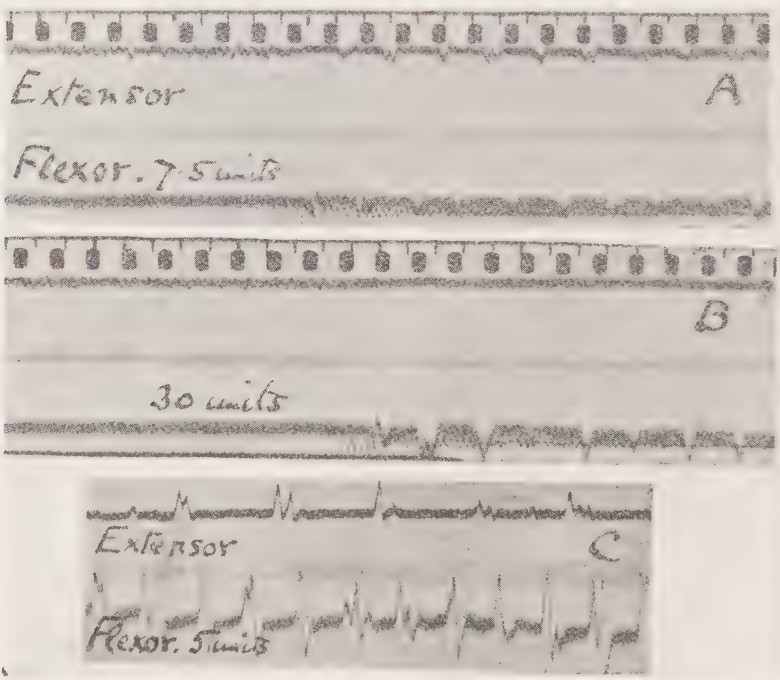

FIG. 139. Simultaneous records of the electrical responses of flexors and extensors of a decerebrate cat during inhibition of extensor contraction, evoked by stimulation of an ipsilateral nerve. (Adrian, *Brain*, vol. 47, p. 410, 1924.)

Evidence of another kind has recently been adduced by Adrian (*9*). He has obtained simultaneous records of the electrical responses of two antagonistic muscles during excitation and inhibition. Thus when leading off from quadriceps and semitendinosus, and the contralateral popliteal is stimulated at 200 per second (see fig. 139), the quadriceps contracts showing in the string record rapid rhythmic vibrations, and the flexor

relaxes giving no electrical responses. When during such stimulation the ipsilateral peroneal nerve is weakly stimulated at a low frequency, *e.g.*, 23 per second the previously inhibited flexors now contract and the galvanometer record from those muscles shows the rhythm of the ipsilateral stimulus. Corresponding in time with these "primary" flexor waves there occur inhibitory pauses in the string record of the extensor muscle. The greater the intensity of the inhibitory stimulus the longer is the duration of these inhibitory pauses in the extensors. This amounts to saying that when a crossed extensor contraction provoked by stimuli at a high rate is inhibited by weak ipsilateral stimulation at a low rate, the rhythm of inhibitory stimulation shows itself in the extensors' electrical responses (*v. supra*, Chapter XIII). The point of added interest is that the rhythm in the extensor muscle dovetails, so to speak, with the rhythm in the flexor muscle. This is readily understood if one analyzes the effect of the first inhibitory stimulus of the series. The first electrical response is seen in the flexor muscle, and this is associated with a brief pause in the rhythmic vibrations of the extensor muscle. At the end of the pause there is a small action current. When the duration of the pause is greater than the interval between the successive inhibitory stimuli the extensor may show only half the rhythm of stimulation (*364*).

In explaining these results, on the basis of the interference theory, Adrian (*9*) draws attention to Forbes's (*318*) suggestion that both excitatory and inhibitory after-discharge may possibly be accounted for by the existence of multiple "delay paths" in the grey matter of the central nervous system. A single impulse, according to this hypothesis, entering upon a system of this complexity would set up impulses in each of the branching pathways and, owing to differences in conduction time, would cause the impulses to be spread out in a long series as they converged upon a common destination. According to the theory, this would be true equally of excitatory reflex paths and inhibitory reflex paths. Increasing the strength of excitatory or inhibitory stimulation merely increases the number and resulting complexity of impulses which impinge upon a common motoneurone, and the greater the number of impulses, the longer will be the *duration* of this convergence. Adrian (*9*) points out that his results and those of Beritoff (*70a*) emphasize how brief the inhibitory effect *may be* when the inhibitory stimulus is weak, and that this brief inhibitory effect synchronizes exactly with the discharge from the antagonistic motoneurones of the flexor centre. "This suggests that the inhibitory pause is due to the arrival at some specialized part of the arc of an impulse or series of impulses of the same type as those which produce the motor discharge and set up

by the same type of central process" (*9*), p. 412). It is then pointed out very justly that while we have no knowledge of specific inhibiting substances which might be set free at synapses in the grey matter, we are quite familiar with that depression of function which follows in the wake of an impulse in a nerve fibre. If, then the conduction along central paths is anything like that in peripheral nerve, an impulse travelling towards a motor centre would, for a brief interval, leave the path which it traversed unfit for the conduction of other impulses, and this easily furnishes a basis for comprehension of the central inhibitory process. The schema shown in figure 137 is given by Adrian and the particular problem in hand, namely, that of explaining reciprocal innervation, is discussed on the basis of the diagram. The principles involved are similar to those outlined in the above quotation from Lucas' (*665*) monograph.

A discussion of the interference theory. Further consideration of the various possibilities of the interference theory have been given by Forbes in his review of spinal reflexes (*318*). For example, the phenomenon of algebraical summation of excitatory and inhibitory reflexes, and the fact that a single excitatory stimulus may often "break through" a precurrent inhibitory stimulation, have been very satisfactorily dealt with. Both Forbes and Adrian (*9*) discuss with great fairness many of the difficulties which beset such a theory of central inhibition in the present state of knowledge. Several additional points, however, may be mentioned which do not appear to favour the interference view, and several of these are points which have been used by the supporters of the theory.

1. Howell (*501*) has recently directed attention to the fact that Vészi's (*1001*) observation on the stimulation of posterior roots has not the significance which many have attached to it (*e.g.*, *665*, p. 96). Vészi is usually quoted as having found that, whereas stimulation of either the ninth or the tenth posterior roots of the frog causes reflex excitation, stimulation of the two simultaneously leads to reflex inhibition. Actually, however, this was not Vészi's (*1001*) observation. What he *did* observe was that stimulation of the cut central ends of either the ninth or tenth root cause contraction of the gastrocnemius, the tenth root yielding a less ample response than the ninth. The seventh and eighth in the majority of preparations, produced no effect at all. When the strength of stimulus was sufficient to give reflex contraction, combined stimulation of two roots (which singly yielded excitation) *gave rise only to summation*, *i.e.*, stimulation of the ninth and tenth roots together always give a more ample contraction than that elicited by either singly. In a few experiments, he did inhibit the reflex contraction elicited through the ninth root by stimulation of the tenth; but it was neces-

sary in obtaining this result to stimulate the tenth root so weakly that when taken alone it gave *no motor effect*. Similarly, stimulation of the seventh root, which readily inhibited the reflex evoked from the ninth, caused no contraction when stimulated alone. What Vészi's result really suggests,—and this on *a priori* grounds seems inevitable,—is that in any given posterior spinal root there is really an admixture of inhibitory and excitatory afferent fibres, and that in any given root one or the other of the two may predominate, if not in number, at least in their reflex effect. It would appear for example, that in the seventh root the inhibitory fibres predominate, and consequently, are able to quell excitatory effects produced through the ninth root. This interpretation of Vészi's experiments is supported by the experiments of Baglioni (*45*) and, though somewhat less directly, by those of Beritoff (*74*) on reflex reversal. Baglioni's results (frogs) are also in accord with the similar experiments of Sherrington (*908*) on the scratch reflex (dog). Baglioni found that when two stimuli, one of which is nocuous, and the other biologically useful, are applied to a frog the nociceptive reflex prevails,—a result in keeping with the well-established conceptions of the "final common path" (*903, 904*). When, on the other hand, two stimuli are applied, both of which are useful or both nocuous, the reflex effects are summated when the two stimuli are applied in the same reflex zone. By the use of such skin stimuli one avoids the complication involved in stimulating a collection of functionally different sensory fibres, such as occur in a posterior root. From these considerations it is evident that Vészi's experiments cannot legitimately be urged as favouring the interference theory, for when two *homogeneous* groups of excitatory fibres are stimulated the result appears to be invariably summation. This objection also applies to the experiment of Tiedemann (*979*).

2. The interference theory gains a certain logical strength from its ability to explain central nervous system phenomena without added assumptions of processes differing in kind from those recognized in peripheral nerve and muscle tissues. If the central nervous system were constituted of these same tissues and no others, this consideration might be decisive in its favour, on the principle of avoiding unnecessary assumptions; but in view of certain recognized anatomical and physiological differences, the failure to consider these differences constitutes in the minds of many a weakness rather than a strength of the theory. For example, in addition to the axons of nerve cells together with the terminations of those axons (which peripheral tissues share in common with reflex arcs), there are the dendrites, even more important, the *nerve cell bodies* or perikarya, and reflex arcs always traverse

them.[2] Within the body of the nerve cell are structural elements and substances which are evidently concerned with the activity of the cell. As Macdonald (*673*) has emphasized, Nissl substance is found concentrated in the dendrites and body of the nerve cell but never in the axon, being apparently limited in its distribution by the boundary of the axon hillock. Mott (*723*) regards Nissl substance as an artefact of the staining process, but his failure to demonstrate it in the living cell is purely negative evidence, and is outweighed by its constant distribution and its tendency to disappear during functional activity (see especially Dolley, *244*, and Hopkins, *498*). The fact that it disappears during activity strongly suggests that it may be of importance in setting up impulses. A striking physiological difference between peripheral and central conduction is the great dependence of the latter on the integrity of the blood supply. As Sherrington has pointed out (*936*), "the contrast between the grey matter's wealth of blood-supply and the white matter's poverty in that respect allows the inference that a chemical activity exists in the former which is lacking in the latter, dealing as this latter does virtually with nerve fibre reactions alone" (p. 543).

In general, therefore, the critics of the interference theory feel that in not recognizing the differences between central and peripheral conducting paths, the protagonists of the interference theory have omitted a vital consideration.

3. The effect of a single inhibitory break shock may continue, as Ballif, Fulton and Liddell (*48*) have shown in examining the spinal knee-jerk, for a period varying from 1 to 4 seconds. This condition of depression frequently involves all of the motoneurones participating in the knee-jerk. If inhibition is conditioned by the duration of the refractory period (3 to 4σ) along central paths (Adrian, *9*), it would mean that the single afferent stimulus had caused the impingement of approximately 400 to 1,600 volleys of

[2] One reason why many investigators have left out of consideration the nerve cell body as an element in the reflex arc, is that in the posterior root ganglia the bodies of the nerve cells are *sidetracked*, giving rise to the so-called monopolar nerve cell. The dendrites in such cases have become functionally united with the axons so that the nerve cell body possibly does not directly transmit the impulse. Moreover, in the case of certain ganglion cells of the crab in which similar monopolar cells are found, Bethe (*95*) observed experimentally that removing the nerve cell bodies did not interrupt a particular reflex action, and similar, though less convincing experiments of the same kind were carried out on the posterior root ganglia of the frog by Steinach (*966*). It must be realized, however, that these are sensory neurones, in which the setting up of impulses always occurs at the terminal end of the dendrite. In motoneurones, on the other hand, impulses appear to be initiated within the nerve cell body. Despite the monopolar character of most vertebrate posterior root ganglion cells Erlanger, Bishop and Gasser (*286*) find that impulses are slightly delayed in passing through them ($\pm 0.1\sigma$)

impulses upon these motoneurones, and at such a rate of repetition as to render them continuously inexcitable. The inherent improbability that such a condition of affairs obtains during the inhibition of the spinal knee-jerk suggests that the interference view is not adequate to account for these results.

4. When the intensity of a single break shock inhibitory stimulus is weak, the stimulus is found to be most effective when it occurs synchronously with the excitatory tap stimulus used to elicit the knee-jerk. This means that the inhibitory stimulus takes it effect immediately, *i.e.*, within 2 to 3σ, (1σ of which is to be accounted for by conduction time) and that it is capable of inhibiting a *single volley of impulses* such as gives rise to the decerebrate knee-jerk. Thus, a single volley of inhibitory impulses can inhibit a single volley of excitatory impulses, either when the inhibitory volley is set up *before* the excitatory volley, or when set up synchronously with it. Inasmuch as the brevity of the knee-jerk latency renders it highly improbable that numerous synapses are traversed in evoking the reflex, it is likely that the seat of inhibition is in (or surrounding) the "final" motoneurones. The observation that inhibition of the knee-jerk is sometimes effective when the inhibitory stimulus falls several sigmata *after* the tap, indicates that *in these cases the seat of inhibition is certainly in or surrounding the final motoneurones;* otherwise the inhibition could not be effective and have such time relations. It would seem impossible to harmonize these observations with the interference theory, since the time relations are too brief to allow of the *repetitive* discharge, which this theory demands.

5. Those who favour the interference view place much faith in Beritoff's (*70a*) demonstration of the brevity of the inhibitory process. It must be remembered that Beritoff's observations are based on galvanometer string records alone, and are therefore, owing to the asynchronous nature of reflex responses, subject to the criticisms of Forbes and Olmsted (*323*); but quite apart from this the fact remains that in spinal preparations, reflex inhibitory effects are ordinarily not of this brief duration (*e.g.*, *936*, p. 531) even with very weak inhibitory stimulation. This has been demonstrated by mechanical records, in the face of simultaneous electrical records which of themselves gave little evidence of the fact (*364*, *48*).

6. The assumption that branching delay paths are responsible for long continued after-discharge, such as occurs even in the responses of deafferented muscles, is unlikely for the following reasons: (*a*) After-discharge of 5 or 6 seconds duration is sometimes observed in the crossed extensor response of the deafferented quadriceps (*160*, *925*), and for impulses to be delayed to this extent at the rate of conduction in mammalian

nerve, it would be necessary for the impulses to travel for a distance of 500 metres, *i.e.*, for more than a quarter of a mile. Even with due consideration of the known complexity of central nervous paths and possible synaptic delays, this would almost amount to an impossibility. (*b*) The mechanical responses of knee-jerks have shown that short tetani do occur in response to single *homogeneous* volleys of stimuli and that the full quota of the responding fibres begin and cease their contraction with approximate (but not absolute) simultaneity. The afferent volley of impulses in the knee-jerk would probably not be sufficiently numerous to give rise to extensive "convergence;" in fact it is likely that the reverse condition obtains, *viz.*, the motor fibres responding are more numerous than the afferent units stimulated. It might be urged that each afferent neurone functioning in the knee-jerk has extensive connections with many motor neurones, but this is unlikely on account of the intensely localized nature of stretch reflexes,—only the particular part of the muscle stretched responds (Chapter XV). One may also recall in this connection the brief latency of the knee-jerk. This again is difficult to harmonize with the assumption of delay paths as responsible for after-discharge. Similar criticisms have recently been offered by Bremer et Rylant (*155b*).

7. Perhaps most difficult of any of the observations on the inhibitory process to harmonize with the interference view is that described in the last chapter, namely, that the early part of the "stimulation-plateau" of a crossed extension reflex is more difficult to inhibit than a later part of the "stimulation plateau," and that the "stimulation plateau" is always more difficult to inhibit than the "after-discharge plateau." It will be remembered that the same motoneurones, both individually and in the aggregate, appear to participate during the "stimulation plateau" as during the "after-discharge plateau." This would mean that at different moments of activity, one and the same motoneurone is more difficult to inhibit than at another moment of its activity. This observation, which can scarcely be questioned on any ground, appears for the time being to offer fundamental objection to the interference view. While it is important to remain open-minded, it would seem that even if subsidiary hypotheses are devised to make this observation or any of the previous observations harmonize with the interference theory, the theory immediately loses much of its logical force, which rests primarily on its ability to account for the phenomena of central nervous system activity in terms of known properties of the peripheral nerve and muscle mechanism.

THE "CHEMICAL" THEORY OF EXCITATION AND INHIBITION

The "chemical" (or "humoral") theory of inhibition derived its support in the first instance from observations upon the inhibition of peripheral tissues, particularly the heart. In 1905 Howell (*501*) drew attention to the similarity between inhibition of the heart produced by perfusates containing an excess of potassium and the inhibition resulting from stimulation of the vagus, and he suggested that the normal vagus inhibition of the heart results from an increase in the diffusible potassium in the muscle cells. Though the specificity of potassium as the inhibitory substance of the heart has not received wide acceptance (*189*, *501*), the general conception of the existence of an inhibitory substance liberated by vagal stimulation has been strongly supported by many investigators. Thus Loewi (*651*) has found that when the heart of a frog is inhibited by stimulation of the vagus a substance is given off into the perfusing liquid which, when circulating through another heart, has the power of inhibiting it. Loewi has pointed out moreover, that the activity of this inhibitory substance is suspended by atropin, which is not the case in pure potassium inhibition. Loewi's experiments have been confirmed and extended by Brinkman and van Dam and Brinkman and van d. Velde (*157*) and others (*652*, *778*, *1060*). They have taken advantage of the fact that whereas parasympathetic stimulation causes inhibition of the heart, it also results in contraction of the stomach. They find accordingly that when the circulating fluid, which has passed through the inhibited heart of one frog, acts upon the stomach of a second frog it causes constriction of the stomach musculature. When, however, the first heart is accelerated through stimulation of the sympathetic, the stomach of the second frog dilates. These observations have recently been confirmed on rabbits (*157;* see also Witanowski, *1060*). One has in these experiments a clear instance of an inhibition brought about by the liberation of a specific chemical substance,—a "secretion" produced by nerve impulses. We may now consider how far such a conception of chemical inhibition is applicable to the problem of central inhibition.

The nature of the central excitatory process. In order to study the process of central inhibition, it is essential first to have a clear conception of the nature of reflex excitation. Following a permissible analogy, are we to consider the central nervous system merely as a complex group of intermingling conducting paths such as exist in the large telephone exchange, or may we infer the existence of processes wholly different from mere conducting systems, processes possibly chemical in nature by means of which new impulses are created and controlled?

The fundamental assumption of the "chemical" theory of excitation is that at some point in the reflex arc, nerve impulses give rise to a process which, unlike the propagated disturbance of nerve fibres themselves, *has no absolute refractory phase* and is thus capable of summated response. In such a process, it is assumed that a nerve impulse produces a quantum of exciting agent, which becomes dissipated spontaneously, but less rapidly than the impulse itself. Being without refractory phase, the presence of a quantum of this agent does not hinder the addition of other quanta from the same or from neighboring points, and the amount of exciting agent present at any one time will depend primarily upon the number of nerve impulses which impinge simultaneously or in relatively rapid sequence upon the central excitatory structure. Such, briefly, are the assumptions upon which the chemical view of excitation rests. They are essentially similar to those made by Lapicque in his theory of "addition latente" in muscle and nerve directly stimulated (*600*). For convenience, the excitatory agent may be termed E substance, or simply E. It is assumed that E is multiplied twofold by two impulses following in sequence, being diminished only by the relatively slight spontaneous dissipation of E during the interval between the impulses. In this way the amount of E might, by repetition of successive stimuli to centripetal nerve fibres, rise from below the threshold necessary for stimulation to above a threshold value. According to this, persistence of central excitation after cessation of external stimulation would be accounted for, and the duration of the after-persistence of contraction would be a measure of the extent of E substance produced by a given stimulation. The all-or-none character of the nerve impulse in the nerve fibre, whether afferent or motor, is accepted without qualification, and it is indeed the foundation stone of our conception of central nervous processes. In other words, the central excitatory process, whatever it be in its fundamental nature, is elicited by a single discontinuous process, or by a series of them. This does not imply that the central excitatory process itself must also be all-or-none. It may resemble instead the process occurring in sensory end-organs such as the retina. The morphological locus of accumulation of E may for the time being be left out of consideration.

If one need any justification for the assumption of the applicability of the all-or-none principle to the problem of gradation of activity within the central nervous system, it is amply provided by the beautiful experiments of Porter and Hart (*779*) on the responses of the tenuissimus muscle. They found that when the flexor reflex of this muscle is evoked by gradually increasing intensities of stimulus applied to the posterior tibial nerve, the amplitude of the reflex increases in abrupt increments, never continuously (fig. 140).

Similar results were obtained when the nerve was stimulated directly. The result is thus entirely in accord with the observations of Lucas, Mines, Pratt, and others upon the discontinuities observed as the intensity of a directly applied stimulus is gradually increased.

A schema has been offered by Sherrington (*936*) which renders more simple the visualization of this non-refractory central process (see fig. 141). Let A, A′, A″ be a group of purely excitatory afferent nerves whose stimulation causes contraction of the muscle fibres M, M′, M″, through the central units C, C′, C″. Further let the three fibres A, A′, A″ be of increasingly high threshold, A having the lowest and A″ the highest. A acts on C by a main terminal but it has also a subsidiary terminal to C′ of the central organ, and this secondary terminal produces less of E, stimulus for stimulus, than the main terminal. Similarly, fibres A′ and A″ act upon the three C organs directly and through various subsidiary terminals indicated

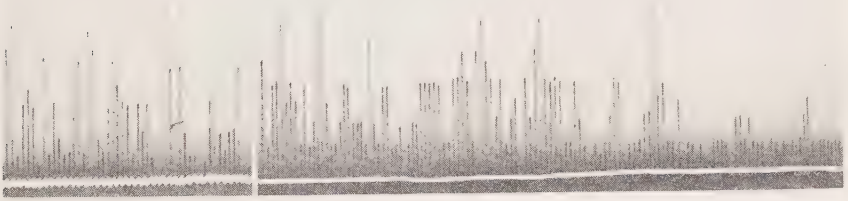

Fig. 140. Reflex (right) and direct nerve muscle responses of the same tenuissimus muscle ("low" spinal cat) as the intensity is gradually increased from below to just above the threshold value. Note the discontinuous steps of increased tension and the close correspondence between increments of contraction in the two records. (Porter and Hart, *Amer. Journ. Physiol.*, vol. 66, p. 400, 1923.)

in the schema. Though for the motor units M, M′, and M″ and for the sensory units A, A′, and A″, the all-or-none principle of reaction is applicable, it does not hold for the excitatory process set up in C, C′, and C″, for this has no refractory period.

Such a picture of the excitatory process renders intelligible the well-known observation that, as the intensity of a single shock stimulus applied to an afferent nerve is progressively increased, there results an increasingly prolonged after-discharge in the individual motor units. It is a legitimate inference that increasingly large numbers of afferent fibres respond as one increases the stimulus intensity. Consequently, even though the centripetal impulses are made up of a single volley, the "convergence" of paths,—a clearly defined histological feature of the central organ (*789;* see below

fig. 202),—will cause many neurones to receive impulses by more than one terminal,[3] and it is evident that the number of impulses converging upon a given C organ will therefore increase with the stimulus intensity. The added amount of E substance produced by this convergence requires longer to subside and in this way gives rise to more extensive after-discharge. The reason for excluding delay paths as an explanation of this after-discharge have already been considered.

If one turns now to the explanation of temporal summation, one finds in this view a ready explanation for the observation that mere repetition of singly ineffective stimuli may in time provide an effective stimulus for a given reflex. "Mere duration of stimulus comes to be equivalent therefore to intensity" (*913*, p. 67). One assumes that the single impulse produces a subliminal amount of E, but that on repetition E may accumulate sufficiently to produce excitation. We have also the fact to explain that in certain reflexes mere repetition of an unaltered stimulus leads to the recruitment of an increasingly large number of motor units. This is readily explicable upon the present view because it is assumed that the subsidiary terminals of our afferent neurone produce smaller amounts of E than the main terminal. Consequently while a single stimulation of A would excite M it would not excite M′; but if the stimulus to A were repeated, it would in time excite M′ by virtue of temporal summation.

"It is with these implications that E is used as a symbol for the central exciting state or agent, and numerals are attached to E for rough quantitative expression of its amount of concentration. C, C′ and C″ in the diagram indicate places at which the amounts or concentrations of E occur. When E at C in what follows has a quantity of 1, its quantity is supposed to be of threshold value for the motor-unit M to which C leads. And similarly for E at C′ and C″. Stimuli delivered to the excitatory afferent are denoted by S when above threshold for A, but below for A′ and A″, by S′ when above for A and A′, but below for A″, by S″ when above threshold for A, A′ and A″. A, A′ and A″'s main terminals provoke individually E of value 1; their subsidiary terminals (broken lines, Fig. 141) provoke individually E of value 0.5" (*936*, p. 524).

With these simple assumptions Sherrington then proceeds to examine in detail the more important experimental facts of reflex physiology. The following example will serve to illustrate his method. Taking the fact that increase within limits of the strength of a single break shock stimulus

[3] This deduction does not conflict with what has been said above concerning the probable absence of extensive convergence in the knee-jerk, for there we were dealing with a homogeneous volley of impulses limited in number and without extensive central connections. When a bare nerve is stimulated the variety and number of afferents brought into play is much greater.

applied to an afferent nerve causes increase of the muscular response, he points out:

"[α] Stim. S, above threshold for A but below for A′ and A″, produces at C an E of value 1, at C′ by A's subterminal an E value 0.5. M's muscle-fibres contract, but M″s do not, nor M‴s.

Stim. S′, above threshold for A and A′ but below for A″, evokes at C an E of value 2, at C′ an E value 1.5, at C″ and E value 0.5. M's and M″'s muscle-fibres contract as before; M‴'s fibres do not respond.

Stim. S″ above threshold for A, A′ and A″ evokes at C an E value 3, at C′ an E value 2.5, at C″ an E value 1.5. M's and M″'s and M‴'s muscle-fibres contract. Hence there is grading of the motor response in accordance with grading of the single-shock stimulus of the afferent nerve" (p. 525).

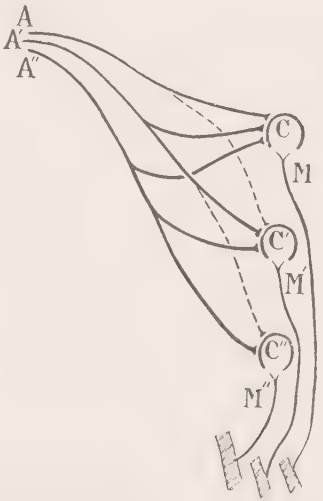

FIG. 141. Sherrington's schema representing his conception of the central excitatory process. For explanation of details see text. (*Proc. Roy. Soc.*, vol. 97B, p. 525, 1925.)

Similarly other reflex data are shown to conform with these simple assumptions. We may note the following: (1) Increase within limits of the strength of a single shock stimulus applied to an afferent nerve increases the after-discharge (*931, 932, 913*); (2) in certain excitatory reflexes mere prolongation of an unaltered stimulus increases the degree of reflex contraction (recruitment, *913, 637, 638*); (3) increase of the stimulus strength within certain limits shortens the latent period of the reflex (*906; 910*, figs. 16, 30, 31); (4) after-discharge both for single-shock and for mechanical stimulation differs greatly in extent in the differing motor units involved; some units in other words fire repetitively many more times than do others

(*637, 931*). All these facts are shown by the same method to conform with the schema. Space forbids a detailed consideration of each datum. Anyone who attempts to work out the various possibilities according to the schema will find his efforts well repaid. We may now turn our attention to the inhibitory process.

The nature of the central inhibitory process. In our consideration of the excitatory reflex, we assumed the production of a specific agent similar to that which has been shown to accelerate the heart. The chemical view of central inhibition is in every way similar to that of excitation. It assumes

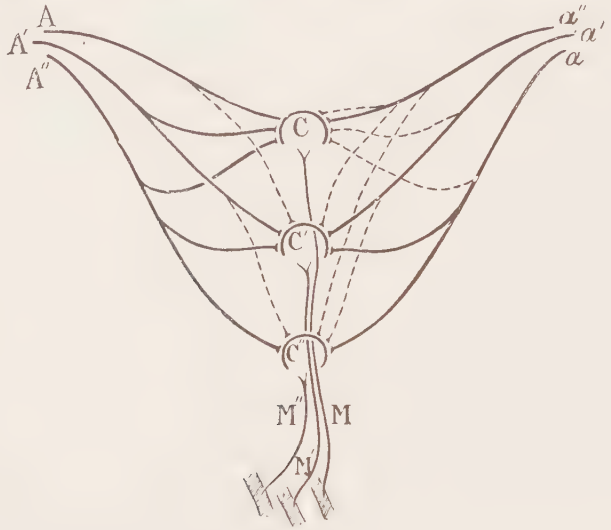

Fig. 142. Sherrington's schema representing the interaction of the central excitatory and inhibitory processes. Note that the inhibitory terminals *a*, *a′*, *a″* are not disposed fully symmetrically about the central mechanism, C, C′, C″, with reference to the excitatory afferents, A, A′, A″. (*Proc. Roy. Soc.*, vol. 97B, p. 528, 1925.)

the production at some point in the reflex arc of an inhibitory substance, I. Let us, as shown in figure 142, visualize a group of afferent nerves, a, a′, a″ which impinge centrally upon the same C organs as do the excitatory fibres A, A′, A″, and let us assume further that the inhibitory fibres (which are of different thresholds) are not disposed fully symmetrically with the excitatory afferents A, A′, A″, in their connection with the central mechanism, C, C,′ C.″ Now we have ample experimental evidence for believing that the after-discharge of inhibition is in every way similar to that of excitation, and we may therefore assume that I substance is produced in

the same way as the E. It is further assumed that the I substance has the power of "neutralizing" E, chemically, electrically, or in some other way explicable in terms of physical chemistry.

It now remains for us to show that a theory of inhibition elaborated on this plan conforms with all experimental data concerning reflex inhibition, and particularly with the experimental data enumerated above which were found out of harmony with the interference view. As with the excitatory reflex, Sherrington has examined the facts of reflex inhibition giving numerical values to the I substance set up by the stimulation of discrete fibres. As a single example of this method of treatment, we may examine the way in which he has explained the fact that mere prolongation or repetition of an otherwise unaltered stimulus applied to an inhibitory afferent increases the extent of the inhibition through inhibitory recruitment (*i.e.*, temporal summation; *936*, p. 536).

"[*θ*] Then, suppose against the reflex contraction produced by stimulus S″, in tetanic form (*i.e.*, giving recruitment) of the excitatory afferent, the stimulus s′ of the inhibitory afferent be used in form of a single shock; at C there will result E6-1 [*i.e.*, E6 minus I1, or E5], at C′ E5-2; at C″ E3-1.5, so that s′ evokes no intercurrent relaxation, although it curtails after-discharge contraction especially in M″. But with s′ as a tetanic stimulus, *i.e.*, obtaining summation, at C there results E6-2; at C′ E5-4; at C″ E3-3, so that the phenomenon of inhibitory recruitment occurs, and an intercurrent "partial" relaxation of the reflex contraction, owing to suppression of contraction in M″, and the after-discharge contraction is much reduced, remaining on M only."

By this method of approach he shows similarly: (1) Increase of the strength of inhibitory stimulation increases within limits the amount of relaxation which the inhibitory reflex can produce in a given excitatory background of contraction (*913*, figs. 4 and 5). (2) The central action evoked by a given inhibitory stimulus produces small relaxation in a background of intense excitatory stimulation and a larger relaxation against a weaker excitatory background (*915*, *918*). (3) After the withdrawal of an intercurrent inhibitory stimulation, there often follows a temporary impairment of the rate of redevelopment of the contraction under continuance of the unaltered excitatory stimulus (*906*, *907*, *911*, *918*, *944*). (4) A corollary of the last effect was shown to conform to the theory; namely, that the inhibitory stimulus more effectually counteracts the excitatory activity of motor units of high threshold for the excitatory afferent than in regard to those of lower threshold for that afferent (*641*, fig. 12). (5) That the stimulation plateau is less vulnerable to an inhibition of given strength than the after-discharge plateau (*641*, *925*). (6) That the latency of reflex inhibition is less with strong than with weak stimuli (*906*, *910*).

(7) That the inhibitory "eclipse" described in the last chapter takes place earlier, other things being equal, the stronger the inhibitory stimulus (*641*). (8) That an inhibitory stimulus delivered during the stimulation period of an excitatory reflex may fail to cause any relaxation and yet in the after-discharge plateau produce an "eclipse" effecting all of the motoneurones engaged in the reflex (*641*). (9) The schema meets the requirement that inhibitory after-discharge persists longer following strong stimulation than following weak, and finally (10) that precurrent inhibitory stimulation, even though it be without effect on the resting muscle, may completely prevent or greatly diminish the response to an ensuing excitatory stimulus. Under this last heading come the results obtained in the inhibition of spinal knee-jerks.

The points of similarity between the postulations required to account for peripheral inhibition and those invoked by Sherrington for central inhibition are very striking. Howell (*501*), in his useful review, has summed up his four main conclusions concerning the peripheral inhibitory process as follows: (1) Inhibition is fundamentally the same process in all (peripheral) tissues and it is likely that a general theory of inhibition may be formulated to cover all cases. It is incidentally important that Howell's review was written before the publication of Sherrington's deductions concerning the nature of the central inhibitory process. (2) Inhibition is produced in all cases through specific inhibitory nerve endings (this also is at the basis of the "chemical" theory of central inhibition). (3) Inhibition is determined by the nature of the ending. Howell points out that the experiments in which motor fibres were forced to regenerate along inhibitory paths and were then found to cause inhibition when stimulated are clearly in harmony with this deduction, and he adds, "It may be supposed that the inhibitory fibres end in a specific physical or chemical mechanism whose reaction to excitation is different from that of the mechanism in which a motor fibre ends" (p. 179). (4) The reaction produced by the terminal mechanism may be chemical or physico-chemical. As a fifth point, it might be added that no valid instance of true reversal of excitation into inhibition (or vice versa) has ever been recorded. The supposed reversal produced by strychnine has been shown, as we shall see in a later chapter, to be due merely to the augmentation of excitatory activity to such an extent that inhibitory effects are thereby smothered (*640*); and there are grounds for believing that the phenomenon of "electrical reversal," so-called, is due to stimulation of morphologically different groups of afferent fibres as the quality of the stimulus is altered (*942*).

DISCUSSION

Having now considered the phenomena of central excitation and inhibition in some detail, we may proceed to a more general discussion and an interpretation of these processes. Evidence has been adduced that both processes have similar characteristics, and that they can exist quite independently of each other. The reasons for Sherrington's belief that the phenomena of excitation and inhibition are explicable in terms of the produc-

tion of specific excitatory and inhibitory substances have also been summarized. His view concerning the excitatory process may be further illustrated by a consideration of the excitatory process in the retina.

It is evident that in the stimulation of the elements in the retina one finds a condition closely resembling that which Sherrington has postulated for the excitatory process of the spinal motor neurone. A ray of light of brief duration is capable of setting up processes, in a limited number of retinal elements, which lead to prolonged repetition of afferent stimuli. Thus, when a flash of lightning occurs, though the duration of the flash is often incredibly brief, one perceives the bright light for a finite period of time—often several thousand times longer than the duration of the stimulus. The image may continue to exist in attenuated form for seconds, or even minutes, as after-images. The radiant stimulus, in other words, has given rise to a long series of repetitive discharges with the result that the brain continues to be affected by the stimulus long after the flash itself has subsided. According to accepted beliefs this prolongation of effect results from localized physico-chemical processes (in the rods and cones) whose function it is to initiate impulses. Such a process is without refractory period. The more intense the stimulus the greater the duration of the chemical activity. It is not a dangerous speculation to assume that intensities of stimulus may occur which do not set into motion sufficient chemical activity to elicit an impulse, but that if several such inadequate light stimuli were repeated at suitable intervals stimulation would result from the summation of chemical effect. In fact there is direct evidence of such an *addition latente* in the case of the eye (*901*, *902*). It is not known, however, whether inhibitory processes exist in the retinal elements; but whether inhibition exists or not, the retinal elements serve as an admirable illustration of the excitatory process.

The comparison of central motoneurones to the receptors of the peripheral nervous system is attractive for many reasons. Embryologically the receptors of the eye are of course a part of the central nervous system, and, though they are highly specialized, it is likely that fundamentally their process of excitation does not differ from other central neurones. Adrian and Zotterman (*19*) in their remarkable analysis of the responses of single muscle end-organs have thrown much light upon the mode of excitation of these receptors. They find that under a *constant* stimulus (stretch) the afferent organ discharges repetitively, and that the *rate* of discharge increases with the intensity of the stretch stimulus. In attempting to account for the repetitive character of the response under constant stimulation, these authors suggest that the end-organ is probably similar to a nerve trunk, save for the fact that the receptor does not readily become "adapted" to the stimulus; a nerve, however, becomes rapidly "adapted," *e.g.*, to a constant current, so that after a single excitation the current is no longer effective as

a stimulus. This hypothesis carries with it the tacit assumption that the "local excitatory process" (*664*) of a nerve trunk is similar to the corresponding process in an end-organ. Though possibly alike as regards an "addition latente" (see p. 350), one must not lose sight of the outstanding difference between these two processes, namely, that whereas, the local excitatory process of a nerve trunk never outlasts the refractory period of the propagated disturbance which it produces (a strong first stimulus never "assists" a subminimal second one, *665*, *330*), the excitatory process in an end-organ (and probably in a central motoneurone) outlasts the refractory period of many propagated disturbances, and also long outlasts the stimulus which produced it. Consequently to attribute to motoneurones and to end-organs the modified properties of their axons, though often suggestive, is probably not wholly justifiable.

This leads us to consider whether or not the excitatory and inhibitory processes of the central nervous system are intra- or extra-cellular.

The conception of inhibition as a process involving electrical or chemical "neutralization" of an excitatory substance makes it evident that the two processes must be able to progress concomitantly in the same morphological situations. Various structural conditions of the central nervous system lead us to suspect that the foci in which these processes co-exist are in or about the perikarya of the neurones. The common focus might, for example, be localized at the surface membrane of the body of the nerve cell or in the dendritic synapses. For many reasons, however, the synapse *per se* is unlikely, for such an interface exists in peripheral nerve-muscle preparations, and yet we do not encounter this type of persistent excitation, nor is it evident that the persistent excitatory processes in the retina are dependent upon synaptic connections. Synapses, moreover,—at least those which exist peripherally,—are not as sensitive to the presence of the circulation as are the conducting elements of the nervous system, which also suggests that they are not the foci of the excitatory process with which we are dealing. It appears more probable on many grounds that the seat of the excitatory and inhibitory processes is within the perikarya of the nerve cell itself.

Ramon y Cajal (*789*, tom. 1, p. 313, fig. 112) has shown that anterior horn cells are surrounded by the "pièds terminaux," of which there are large numbers adherent to the body of the cell. One of Cajal's illustrations of this is given in figure 143. It is possible that some endings convey impulses which lead to the liberation of "E" substance, and others to the liberation of "I" substance within the nerve cell body, depending upon the region of the cell on which they terminate (*936*, pp. 524 and 533.)

The well-marked concentration of Nissl substance in the dendrites and its absence in the axon (*673*, *498*, *244*), together with the fact that the Nissl substance disappears during activity, suggests that the dendrites are con-

cerned with the excitatory process. One might picture the excitatory process as a physico-chemical reaction centering eventually about the axon hillock. The inhibitory process might be visualized as involving a chemical process, which tends to oppose that produced by the excitatory process. One cannot well conceive of two such chemical processes progressing extracellularly, for without the protection of the cell membrane it is difficult to imagine how they would be localized. But it would be unprofitable to place too great emphasis upon purely structural considerations.

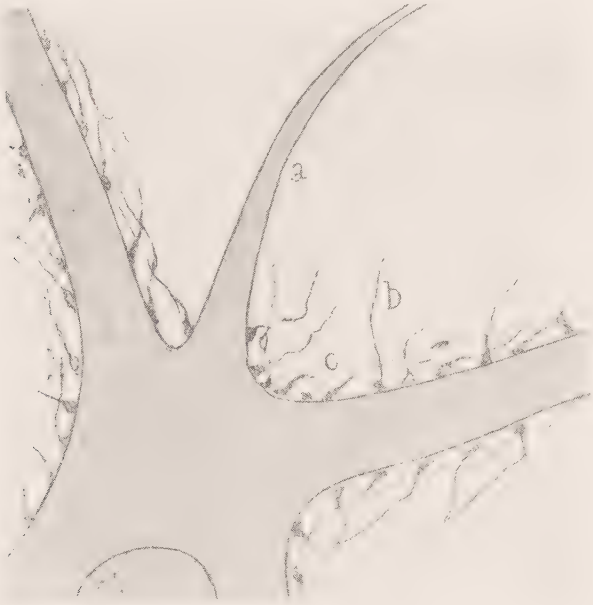

FIG. 143. A rabbit's anterior horn cell showing the axon (*a*), two dendrites, and the so-called "pieds terminaux" attached to the cell membrane. This is the characteristic mode of termination of the "reflex-motor" collaterals, and are found apparently in all anterior horn cells. (Ramon y Cajal, *789*, tom. 1, p. 313, 1909.)

An important practical outcome of the theory of chemical excitation will be the determination of the rate of discharge of the individual motoneurones. They are subjected to a form of stimulation which is supramaximal in the sense that the E substance responsible for it is produced in excess. The presence of such an excess within the central unit might lead either to discharge of impulses at a (constant) maximum frequency, or at a progressively diminishing frequency as the concentration of E substance falls. The experiments of Querido (*787*) suggest that ganglion cells of the sympathetic

discharge at a constant rate when maximally excited; the observations of Forbes and Olmsted, on the other hand, would lead one to suppose that the rate of discharge of spinal motoneurones is variable. This also raises the question of whether neurones under these circumstances discharge so

FIG. 144. A more general view of the mode of termination of collateral fibres within the cord of a cat. (Ramon y Cajal, *789*, tom. 1, p. 311, 1909.)

rapidly that the impulses passing down the nerve fibre are subnormal in magnitude, or does the axon hillock so regulate rate of discharge as to ensure that the interval between stimuli will be sufficient to allow of all impulses being of full size? These questions we propose to consider more in detail in a later chapter on voluntary contraction.

It may be objected to the chemical view of excitation and inhibition that it reduces the afferent neurones to mere "secretory" fibres, yet this is essentially the nature of the nervous production of excitation and inhibition in peripheral tissues such as the heart. Moreover, as Sherrington pointed out in 1906, "it appears unlikely that in their essential nature all forms of inhibition can be anything but one and the same process" (*910*). Critics of the interference view of inhibition accordingly find difficult the separation which it makes between various forms of inhibition. Thus, not only do they separate peripheral and central inhibition as two wholly different

FIG. 145. Anterior horn cells of a new-born dog, showing the extent of the ramification of their dendritic processes throughout the substance of the cord. (Ramon y Cajal, *789*, tom. 1, p. 357, 1909.)

processes, but they even suggest that various different forms of inhibitory process may exist in the central nervous system itself. Adrian (*9*), for instance, has intimated that such inhibition as occurs in the reciprocal innervation of antagonistic muscles may be quite different in nature from the inhibitory control exerted on the cord by the higher centres. The "chemical" view, on the other hand, has the advantage of reducing all forms of inhibition to one and the same fundamental process.

SUMMARY

Skeletal muscles are without peripheral inhibitory nerves, commencement and cessation of activity being conditioned solely by central nervous control. Since muscular activity is our most valuable index of central processes, we must rely upon muscular responses in order to study central inhibitory processes. In this chapter the two more important theories of central inhibition have been discussed.

According to the interference theory, central nervous pathways are conceived as possessing properties similar to those observed in isolated nerve. Since it has been found that, when nerve trunks are stimulated above a certain critical frequency, conduction ceases across regions of subnormal conduction (*e.g.*, the neuromyal junction), it has been assumed that similar "interference" occurs along central nervous pathways, and, under appropriate circumstances, that this leads to cessation of activity, *i.e.*, to central inhibition. This theory has the logical advantage of postulating nothing beyond the properties already demonstrated in isolated nerve. However, when applied to account for the phenomena of central inhibition, this theory is not wholly adequate. In the first place, it cannot explain the fact that an inhibitory stimulus is most effective in inhibiting a knee-jerk when it falls synchronously with the knee-jerk stimulus. Accurate measurements have shown that an inhibitory stimulus takes its effect within 2 to 3σ of the time of its application to an afferent nerve. The depressing effect of such a stimulus, moreover, continues to exist for 1 to 4 seconds, during which time all, or the majority of the anterior horn cells supplying the muscle are rendered completely inactive. To explain this on the grounds of interference, it would be necessary to postulate the impingement of 400 to 1600 volleys of impulses at 400 to 500 per second. The interference theory has also been shown to fall down when applied to other important phenomena in reflex physiology.

The alternative theory, namely that of "chemical" inhibition, postulates the liberation, within or about the perikarya of nerve cells, of a specific inhibitory substance which antagonizes a similar specific excitatory substance produced at the same morphological region. The assumption of such depressant qualities serves as an adequate basis for explanation of all of the phenomena of reflex physiology at present recognized. It may be pointed out that the specialized excitatory and inhibitory processes, here assumed, having no refractory phase, have a parallel in the local excitatory process as defined by Lucas and Lapicque. The excitatory process in the central nervous system is conceived of as being more prolonged and capable

of more extensive temporal summation than the local peripheral excitatory process. It is emphasized that all reflex arcs involve functional units not encountered in the nerve-muscle preparation, namely, the nerve cell body. The changes which this structure undergoes during activity or during asphyxia, together with the well-recognized changes observed in the functional activity of central conducting paths under such conditions, suggests that the nerve cell bodies are in fact the loci of the central excitatory and inhibitory processes. It is pointed out that their behaviour appears to be in every way comparable with such receptor neurones as are found, for example, in the retina of the eye. Consequently, the assumptions made are not *ad hoc*, but have well-recognized parallels in the receptors of the nervous system.

Addendum. After this volume had gone to press Samojloff and Kisseleff's important paper on the inhibition of the flexor reflex was read at the International Physiological Congress at Stockholm (*Abstracts of Communications*, p. 145). They have observed in the semitendinosus muscle (decerebrate cat) that the flexor reflex elicited by a single break shock may be inhibited by a single contralateral break-shock stimulus, even though the latter fall 100σ or more *before* the (ipsilateral) excitatory stimulus. This again emphasizes the prolonged character of central inhibitory effects, and on the basis of it and other evidence these authors conclude that central inhibition must be brought about by the liberation of an inhibitory substance at some point in the reflex arc. The observations are of especial importance since the excitatory volley of impulses in their experiments was definitely *single*, and there was no possibility, as with the knee-jerk (*v. sup.*, p. 287), of repetitive afferent responses. Professor Samojloff informs me that their paper will appear in due course in Pflüger's Archiv.

CHAPTER XV

Reflexes in Response to Stretch (Myotatic Reflexes)

A common experience to those who are familiar with the decerebrate condition in man or animals is the resistance encountered when attempting to impose upon a limb a new posture. Careful examination reveals that this resistance to passive movement is most prominent in antigravity muscles of which the extensors of the knee are a classic example. The resistance encountered under these circumstances suggests that certain muscles respond to the pressure imposed upon them by active contraction. These observations led Liddell and Sherrington (*639*, *640*, *935*) to study the phenomenon, which proved to be a "stretch" or myotatic reflex. Their investigation of this phenomenon provides a beautiful example of modern physiological analysis, and it is proposed in this chapter to dwell fully upon the development of their argument.

To investigate the stretch reflex it is necessary to isolate the particular muscle used from outside muscular influence. For this purpose the quadriceps of decerebrate cats were employed; in both limbs the sciatic, pudic, internal saphenous, obturator, external cutaneous and the groin nerve of fourth lumbar root were cut, as well as the femoralis of the limb opposite to that used (for full description, see Appendix). Further the rotators of the hip joint on both sides and other muscles in this region (the psoas magnus and parvus, the glutaei, quadrutus and gemelli, the obturator, pectineus, tensor fasciae femoris muscles) were severed from their insertions. The sartorius, which was paralyzed by nerve section, and the tensor fasciae femoris on the ipsilateral side were freely cut away to avoid their participating mechanically in the stretch applied to the quadriceps which lies beneath them. These precautions leave the quadriceps on the side on which observations are made the only structure in the hind limb still retaining its sensory connection with the central nervous system. The only sensory nerves which could possibly modify the reflex activity of the muscle are those in a limited region at the base of the tail, but the preparation was so set up with clamps and drills that the tail and the back did not touch the experimental table. It is clear, therefore, that any reflex effect produced by applying stretch to the patellar tendon is wholly confined to the quadriceps muscle. In these experiments the hind limb and pelvis of the

preparation were firmly fixed to a rigid table by means of clamps and drills. The table was capable of being lowered at any desired speed, and perfect regularity of motion was ensured by means of a controlling oil piston. The patellar tendon was attached by a tempered steel hook *directly* to the optical isometric myograph.

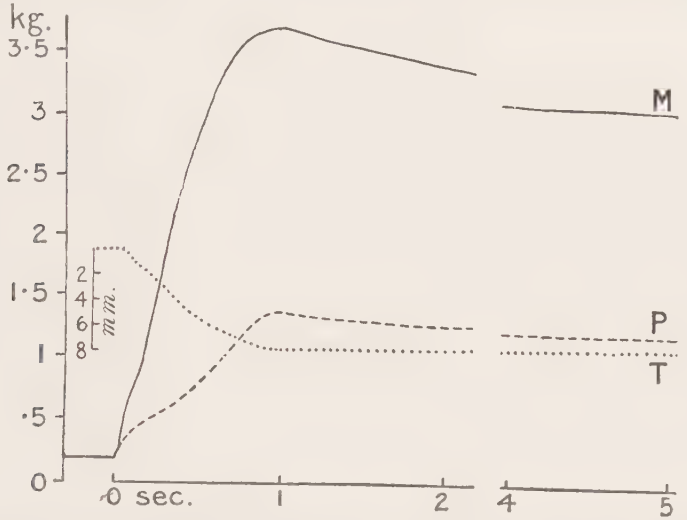

FIG. 146. Whole quadriceps of decerebrate cat. Muscular response to 8 mm. table-stretch T before (M) and after (P) cutting nerve to muscle. Myograph multiplies tendon-movement 62 times. Time in seconds. The rate, duration and extent of the stretch is indicated by the line of round dots. (Liddell and Sherrington, *Proc. Roy. Soc.*, vol. 96B, p. 213, 1924.)

SEPARATION OF THE REFLEX CONTRACTION FROM THE PASSIVE TENSION INCREASE OCCASIONED BY THE STRETCH

When a quadriceps muscle of a decerebrate animal, prepared in this way (and placed under 50 to 100 grams initial tension), is gradually stretched,—for example, by 3 mm. in 2 seconds,—the myograph rises rapidly to a maximum tension and then gradually descends after the stretch is discontinued (fig. 146). The increase of tension in the muscle, occasioned by the stretch, might be due merely to the passive increase in tension resulting from the application of force to the tendon. That this is not the case is evident from the fact that (1) the passive tension curve resulting from elongation of denervated muscle is of wholly different shape from that of the curve described by the quadriceps muscle under these circumstances (see figs. 146 and 147). (2) When the muscle is stretched,—starting at the same

initial tension,—after the nerve to quadriceps is severed the myograph rises only a small fraction of the amount which it rises when the nerve supply of the muscle is intact and "tonus" is marked. (3) Similarly, when the posterior roots have been severed the muscle, on stretching, behaves as though its nerve were severed (fig. 148). (4) Much more convincing

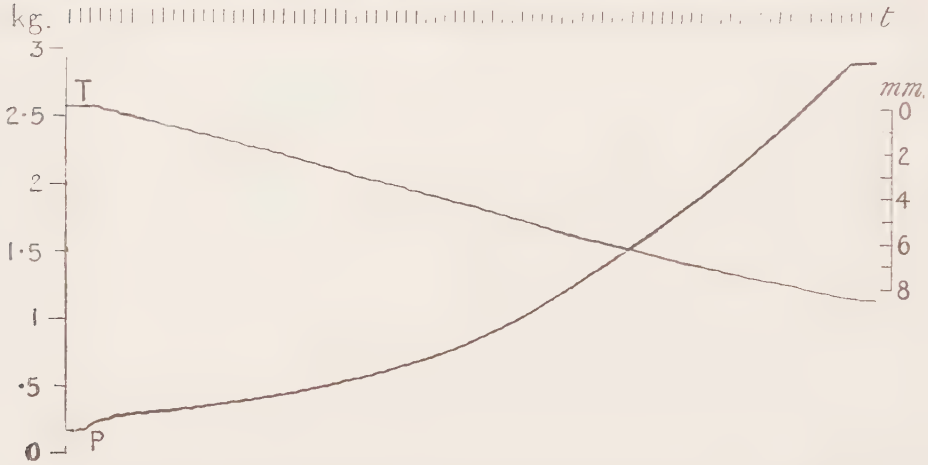

FIG. 147. *Vastocrureus.* P response of muscle after section of its nerve to T a gradual 8.5 mm. table-stretch: *t* in $\frac{1}{10}$ second. Myograph multiplies tendon-movement 62 times. (Liddell and Sherrington, *Proc. Roy. Soc.*, vol. 96B, p. 215, 1924.)

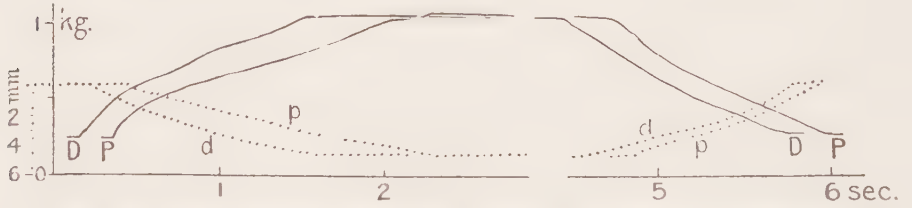

FIG. 148. Whole quadriceps deafferented 112 days. Comparison of deafferented D and paralytic P (*i.e.*, after nerve-section) muscle to two comparable 5 mm. table-stretches, *d*, applied to deafferented, *p*, to paralyzed muscle. Myograph multiplies tendon-movement 42 times. Time in seconds. (Liddell and Sherrington, *Proc. Roy. Soc.*, vol. 96B, p. 217, 1924.)

evidence of the reflex character of this response is the fact that it can be *inhibited*, as can other extensor reflexes of quadriceps, by stimulation of any ipsilateral sensory nerve to the hind limb. Such an inhibitory stimulus, if of adequate strength, may bring the myograph completely down to the level of the new base line imposed by the passive elongation of the muscle. If the inhibition occurs before the stretch is applied, the muscle describes a

curve similar to that of a muscle whose motor nerve has been cut (see fig. 149). In other words, an inhibited muscle behaves as a denervated muscle. From these four lines of evidence Liddell and Sherrington concluded that the reaction of the quadriceps muscle to passive stretch is an active reflex contraction. We may now consider the properties of this reflex in greater detail.

CHARACTERISTICS OF THE STRETCH REFLEX

Source of the reflex. The complete denervation and tendon resection of all other structures in the two hind limbs makes it evident that the sensory channels of this reflex in all probability lie within the muscle itself. The skin of the foot and the leg of the skin covering the muscle is completely anaesthetic and the skin of the back and tail is not affected by the passive increase of tension. One may ask, therefore,—since the sensory organs of the reflex lie within the muscle itself,—"In what portion of the muscle are these endings found?" The stretch reflex was found to occur after the patellar tendon had been anaesthetized with novocaine, or even after the tendon had been completely cut away, and one may still elicit the reflex if the belly of the muscle is attached to the myograph by a tight and even destructive ligature tied well proximal to the tendon. The reflex, in other words, is elicited by the stretch of the muscle fibres themselves. The numerous sensory organs known to occur in the tendon and tendinous aponeuroses are therefore not necessary for the elicitation of the stretch reflex, and they may subserve other sensory functions (*898*, *639*, *935*).

Phases. Myotatic reflexes tend to consist of two modes or periods of reaction: (1) The "phasic" or short lasting and relatively intense reaction confined largely to the mechanical ascent of the reflex, that is, the period during which the stretch is applied; and (2) the "postural" or tonic period less powerful but longer lasting (fig. 146). These, as Liddell and Sherrington have pointed out, may be distinguished as the phasic contraction and the postural contraction. The postural contraction of this reflex is that which occurs under constant pull (*i.e.*, without altering the length of the muscle). It is, in other words, "static," being confined largely to the period after the stretching table has ceased to fall. It must be emphasized that the phasic period of the stretch reflex is not confined exactly to the period during which the table falls, for the myograph continues to ascend for a short time after cessation of the stretch stimulus (for a period equal roughly to the ascent of a knee-jerk). The postural contraction of the reflex commences, therefore, not after cessation of the stretch but immediately after the phasic or kinetic period has ceased.

The second, or postural phase of the stretch reflex is of great importance on account of its long continuance. A muscle may be left under stretch for a long period of time and tested at various time intervals for the existence of this postural element of the reflex by the application of any inhibitory stimulus. Liddell and Sherrington observed that a postural contraction may remain for a period of at least a half hour without apparent fatigue. It will be seen in figure 146 that the "plateau" of the reflex tends gradually to diminish in height. When, however, the stretch reflex is allowed to continue for a long time the height of the postural contraction diminishes at first and then reaches a condition of steady equilibrium. The sloping of the initial portion of the reflex is more pronounced when the stretch is delivered rapidly, and is probably, therefore, due to the "lengthening reaction" (Chapter XVII). The phasic portion of the reflex is, in other words, more pronounced in response to rapid stretch than when the stretch is delivered slowly.

Various other factors tend to modify the relative importance of the two stages of the stretch reflex. If the animal is made spinal the phasic portion of the reflex is still present in the form of a knee-jerk, but the postural element is difficult and usually impossible to demonstrate. In one preparation which had been made spinal aseptically five days previous to the experiment a small postural contraction was observed (*48*), which was capable of being inhibited, but this soon disappeared in the course of the experiment and could not be again elicited. This, however, would tend to support the conclusion of Viets (*1002*) that in the spinal condition all the necessary elements for the manifestation of tonic activity are present, and that tonicity can be simulated by contralateral stimulation. The observation is also in harmony with the well-known fact that a certain measure of tonicity returns to "chronic" spinal animals at varying intervals after the transection, and with Sherrington's (*919*) discovery that "shortening reactions" are to be obtained from (chronic) spinal dogs (see Chapter XVII).

Intensely local nature of the reflex. Until recently it has been customary to believe that the various reflex centres of the spinal cord act as a unit (Camis, see *843;* Sassa, *843* (1), Adrian, *17;* Graham Brown, *103*), the flexor centre involving all the flexor muscles, as in the familiar flexion reflex, and the extensor centre similarly involving the extensor muscles. These centres were believed to act always *en masse*, being incapable of fractional activity. A stretch reflex provides an example of the direct antithesis of such a condition. If the quadriceps muscle is divided into its four constituent parts, it is found that only the part stretched responds by active contraction. If rectus is stretched, rectus and only rectus responds. More-

over, if a portion of the rectus is cut away and that portion is stretched, it contracts and the remaining portion remains inactive.[1] The stretch reflex, in other words, is intensely local in its reflex effect, being capable of minutely fractional degrees of activity; presumably the smallest unit of activity is the single "stretch-afferent,"—whatever it may be morphologically,—and the group of muscle fibres which it controls reflexly. The proportion of sensory to motor nerve fibres in a purely muscle nerve is approximately 1 to 2 (Sherrington, *880*), though in some nerves supplying muscle the sensory and motor fibres are approximately equal in number. Thus, Hay (*445*) found that in a rabbit's semimembranosus supplied by 1143 fibres, only 547 were efferent. However, as all the sensory fibres do not supply stretch-afferents, the ratio of stretch-afferents to motor nerve fibres possibly may not be more than 1 to 4 or 5. One would therefore visualize the smallest reflex unit of these myotatic reactions as one stretch-afferent with its 4 or 5 motor nerves and the muscle fibres which they govern.

The problem of the number of muscle fibres supplied by one medullated motor nerve fibre is interesting and important on account of the strict limitation which it imposes upon the degree of fractionation of activity of which the central nervous system is capable. In the case of the tenuissimus muscle, adequate data is available for such a calculation, and it gives us the following somewhat surprising relation, namely, that there is only one nerve fibre to about 100 to 150 muscle fibres. Graham Brown (*163*) and Adrian (*13*) have observed that the number of medullated nerve fibres in the main nerve trunk supplying tenuissimus varies between about 55 and 95, with an average of approximately 75. Of these, probably a third are sensory (*779*),—at least if this nerve resembles other muscle nerves in the cat (*880*). Consequently, we may believe that not more than 50 are motor. Now Porter and Hart (*779*) state that an average cross-section of tenuissimus reveals approximately 1000 muscle fibres, but, since Adrian (*13*) has shown that the average length of muscle fibre in tenuissimus is only 17.3 mm., and since the average length of the whole muscle is 7 times this (*i.e.*, 120 mm.), the muscle must contain at least 7000 fibres. This gives a ratio of 50 to 7000, or 1 to 140 nerve to muscle fibres. A small accessory nerve twig often passes to tenuissimus near its tibial end, which would somewhat diminish this ratio, but no one has counted its fibres. The arrangement of the fibres in tenuissimus is given above in figure 21 A (Chapter I).

In the m. cutaneus dorsi of the frog, investigated by Lucas (*661*), the figures are more satisfactory, there being 9 to 10 nerve fibers, all of which are motor (*19*), and 150 to 200 muscle fibres (*661*). Adrian and Zotterman (*19*) find 10 to 25 fibres in the nerve to m. sterno cutaneus (frog) of which certainly 3 to 5 are sensory, and Reichert (Müller's Arch., 1851, p. 29) states that this muscle contains 280 to 340 fibres. Reichert, how-

[1] This applies to the extensor muscles of acute decerebrate preparations. Magnus (*681*) has recently noted that with intact or with *thalamic* animals stretch applied to one of the flexor muscles of the fore-limb appears to cause reflex contraction of synergic flexor muscles which were not actually stretched.

ever, found only 6 to 10 fibres in the nerve to this muscle. (Cf. also Ranvier, *795*). These figures give ratios of the order of 1 to 15–30.

It is difficult to believe that all muscles are characterized by so high a ratio, especially such muscles as the external oculars in which minutely fractional degrees of activity are so essential (cf. *930, 945*) to delicacy of adjustment. I am not aware that the required information is available to enable a similar calculation for these muscles. It is a matter which well deserves investigation.

Absence of after-discharge. The gradually sloping character of the stretch reflex plateau might conceivably be attributed to a long lasting after-discharge of the phasic period of the reflex. That this is not the case is evident from the fact that the reflex ceases *immediately* the stretch stimulus is removed, that is, if one allows a period equivalent to the duration of the knee-jerk for the last afferent endings stimulated by the stretch to carry out their contraction. We have seen in the previous analysis of the knee-jerk that in the decerebrate condition, it tends to be produced by one or sometimes two volleys of motor nerve impulses, and there is no reason to believe that the after-discharge in the case of the stretch reflex is any greater in extent than in the case of the knee-jerk. It is therefore safe to conclude that the after-discharge is not greater in extent than 1, to 2 or 3 repetitive volleys of inpulses (separated by brief intervals) of the last neuro-muscular elements stimulated immediately before the cessation of the stretch. There is also nothing comparable in the central mechanism of the stretch reflex to recruitment, that is under mere continuance of *static* stretch (unaltered length) there is no progressive increase in the number of units excited. When considered, however, from the viewpoint of the afferent endings a recruitment of these organs undoubtedly occurs under gradual increase of the stretch stimulus. To quote Liddell and Sherrington:

"The build of the quadriceps, especially of its vastocrureus portion, suggests that as the pull on the patellar tendon increases, namely, as the stretch increases, the mechanical stretch involves progressively increasing numbers of the muscle-bands composing the muscle. The increase of the reflex contraction as the stretch proceeds would therefore be explicable by corresponding increase of the number of receptors in the muscle coming under the influence of the mechanical stimulus. This is supported by several features of the reflex contraction. Thus, the increase of contraction goes on fairly equably so long as the stretch continues being equably increased, and all irregularities in the process of the stretch are closely reflected in the contraction ascent. . . . . One thing that the ascent portion of the reflex contraction shows is the extreme delicacy of the grading of the contraction in accordance with grading of amplitude of the passive stretch imposed. Increase of the stretch is accompanied by increase in the number of its proprioceptors stimulated and of the motoneurones excited which supply it (p. 120).

Another proof that the declining plateau of the stretch reflex is not an after-discharge of the phasic reflex is provided in the record shown in figure 149. In this record the phasic portion of the reflex has been separated from the static or postural (see also fig. 150). This was done by inhibiting the muscle during the period in which the table was falling and then allowing the muscle to respond to the static stretch under which it found itself

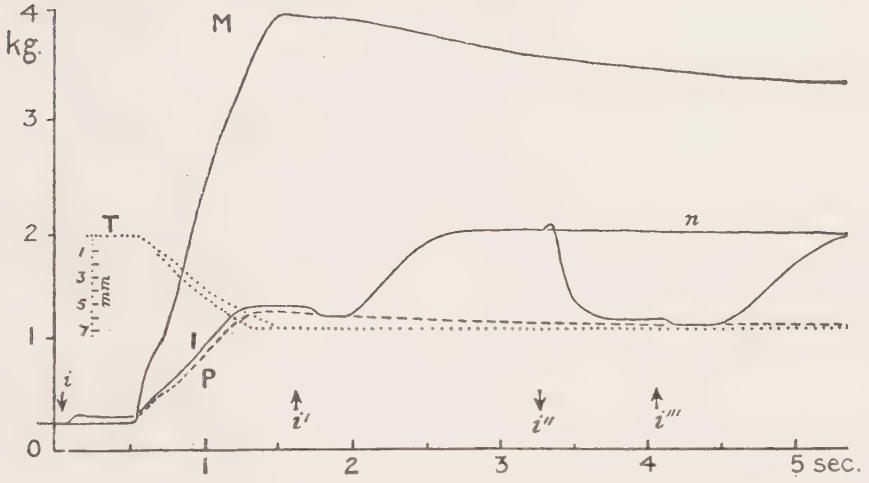

Fig. 149. Whole quadriceps. Successive reactions M of normal, I of reflexly inhibited, and P of paralyzed (*i.e.*, after nerve-section) muscle to table-stretch T of 7 mm. The inhibition (by ipsilateral afferent peroneo-popliteal nerve) was on first occasion from i to i', on second occasion from i' to i'' and again from i' to i''', giving therefore on second occasion the fall from and reascent to the plateau line n of the first occasion. The inhibitory nerve gave slight concomitant contraction (see *364*) so that full inhibitory effect is seen only close subsequent to cessation of the inhibitory stimulation. The less steep dotted line T gives the table-stretch for observation M; the other for observations I and P. Myograph multiplying tendon-movement 62 times. Time in seconds. (Liddell and Sherrington, *Proc. Roy. Soc.*, vol. 96B, p. 225, 1924.)

on emerging from inhibition. It is clear from this record that the muscle responded by active contraction, and a proof of this active contraction was provided by subsequent inhibition which occurred in the last part of the record. This experiment, which is of importance, is described in greater detail in the legend to the figure.

An important characteristic of the stretch reflex is its brief *latency*. Sherrington and Liddell concluded from mechanical records that the contraction commenced within at most 20σ from the time of commencement

of the mechanical stimuli. With combined electrical and mechanical records it was later shown (*365*) that the latency of this reflex was of the same order of magnitude as that of the knee-jerk, namely, 6 to 9σ.

FUNCTIONAL SIGNIFICANCE OF THE STRETCH REFLEX

The stretch reflex is not a phenomenon peculiar to a preparation decerebrated at an intercollicular level. Though probably most pronounced in animals in this state, it is nevertheless present in the so-called Magnus

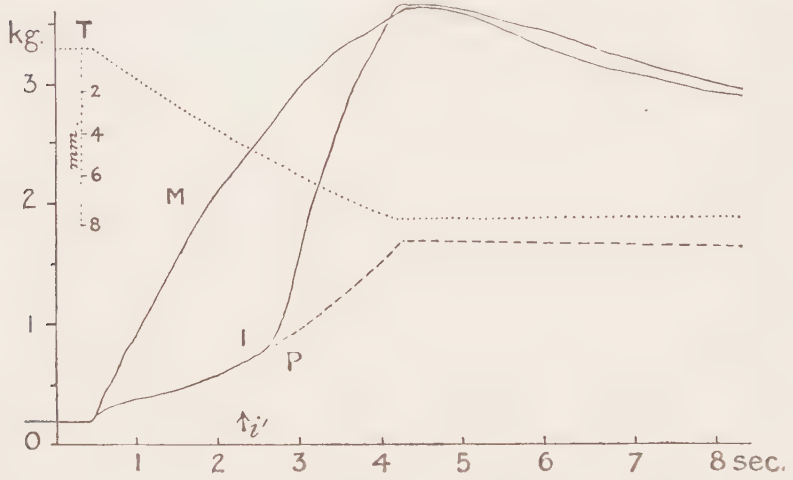

FIG. 150. *Vastocrureus*. 8 mm. table-stretch T. Reaction of uninhibited muscle M, of muscle reflexly inhibited for earlier half of the reaction I and of paralysed (by nerve-section) muscle P (broken line). The stimulation of the inhibitory afferent was begun before the course of the reaction shown in the figure but was discontinued at *i'* in the figure. Myograph multiplying tendon-movement 62 times. Time in seconds. (Liddell and Sherrington, *Proc. Roy. Soc.*, vol. 96B, p. 232, 1924.)

animal, in which the thalamus remains intact (fig. 151). There is, moreover, no reason to doubt that it exists in the intact animal. The occurrence of the knee-jerk and the fact that it (the knee-jerk) is most readily elicited in the normal subject when the muscle is put on the slight stretch, all point to the existence of stretch reflexes in the intact animal.

The fact that these reflexes are largely confined to the antigravity muscles suggests at once an important adaption to functional utility. It is known that a "chronic" decerebrate preparation is capable of reflex standing (*679*, *60*, *927*). Now, it is on the antigravity muscles that the increase of tension necessary for maintaining the weight of the animal against the force

of gravity would first make itself felt, and in this way it would evoke in those muscles a stretch reflex. In the words of Sherrington,

"Elicitation by gravity of the stretch reflex of the limb-extensor suggests itself as a basic factor in this static geotropic reflex of standing. As such it offers an explanation of the postural contraction counteracting gravity, of the proprioceptive nature of that reaction, and of the latitude of detail allowed to the standing posture of the limb" (*935*).

Magnus (*681*) has recently shed new light upon the stretch reflex. He has described what he terms a "positive supporting reaction," a reflex elicitable in intact, thalamic and decerebrate preparations. It is evoked by any gentle pressure on the fingers and toes tending to dorsi-flex the paw. The musculature of the limb then becomes sufficiently stiff to sup port the weight of the body. Cutaneous and proprioceptive stretch stim-

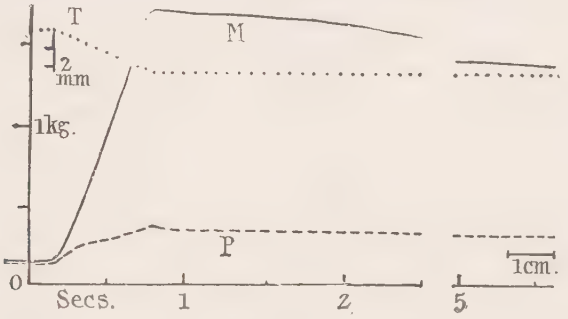

FIG. 151. "Magnus" animal. Responses of quadriceps cruris to table-stretch (T) of 2.5 mm. before (M) and after (P) severance of its nerve. Preparation decerebrated by transection 4–5 mm. anterior to the anterior colliculi. T, record of table-fall. (Liddell and Sherrington, *Proc. Roy. Soc.*, vol. 97B, p. 269, 1925.)

uli both coöperate in the production of the reaction, but it may be elicited when either one of these two sources of stimulation have been excluded by nerve section or tendon resection. For further details the reader may consult Prof. Magnus's illuminating Cameron lecture (*681*).

It may be urged that the extent of the elongation necessary to produce stretch reflex is greater than is compatible with the belief that this reflex is responsible for reflex standing. That this is not the case is indicated by the fact that in walking or trotting of a dog the femoro-tibial joint passes through an angle of about 50°, and in a gallop through an angle of usually 80° (*639*). In the cat these transitions do in fact correspond with the amplitudes of stretch of the quadriceps, which are much above the threshold for eliciting the stretch reflex. In six cats the elongation of rectus produced

by extending the knee-joint from full flexion to extension are shown in table 14 (from Liddell and Sherrington). It is evident from this table that the degrees of elongation produced by movement of the leg about the knee-joint are far greater than is necessary for elicitation of the stretch reflex, for it could be evoked by elongation as small as 0.5 to 2 mm. The percentage increase in length necessary to evoke a stretch reflex may be as small as 0.8 per cent.

Cole (*J. Gen. Physiol.*, vol. 8, p. 253, 1926) has recently encountered stretch reflexes in the snail, *Helix*. He finds that the marked negative geotropism of this animal is a reaction traceable to its muscle proprioceptors, which respond to the stretch imposed by gravity. He observed that a snail loaded by one-half its own weight progressed up an incline of 45° 1.51 times more rapidly than an unloaded animal. Cole's observations show that stretch reflexes are more widely distributed in the animal kingdom than had hitherto been suspected, and they suggest that the tonus of "voluntary" muscles, even among the invertebrates, may have origin in this form of reflex stimulation (see Chapter XVI).

TABLE 14

Length of rectus femoris from the acetabulum to upper border of patella, hip being at right angles to trunk

WEIGHT OF ANIMAL	KNEE FULLY FLEXED	KNEE FULLY EXTENDED
grams	*mm.*	*mm.*
2,370	107	89
2,080	98	78
1,680	88	70
1,665	103	84
1,865	100	79
2,470	108	88

Influence of the flexors on the extensors. In his early investigations on the (spinal) knee-jerk Sherrington (*875*, *876*) observed that tension in the flexor muscles tended to inhibit the amplitude of the knee-jerk, and he observed in addition that even massage of the biceps greatly reduced the size of it. Active contraction of the flexors elicited by stimulation of their anterior root supply also caused inhibition of the patellar jerk. This led Liddell and Sherrington (*640*) to investigate the effect of the flexors on the stretch reflex. They found, in a preparation which had been denervated in the usual way, but in which the hamstring nerve supplying the flexor muscles was allowed to remain intact (fig. 152), that if any one of the flexor muscles were pulled, quickly, or gradually, during the height of a myotatic reflex of quadriceps, the reflex would be inhibited partially or nearly completely according as the stretch of the flexor were vigorous or slight. Even when

vigorous, however, traction on one flexor muscle usually did not serve to inhibit the stretch reflex completely. Certain muscles of the flexor group were more effectual than others; thus biceps produced inhibition more quickly and more nearly completely than semitendinosus (fig. 153) and semitendinosus was more potent than gracilis or semimembranosus. "Rebound" contraction in quadriceps is also inhibited by traction on the flexors (fig. 154); the inhibition of crossed extensor contraction by pulling upon the ipsilateral flexors has not yet been investigated. These observations provide at least a partial explanation for the events which occur in stepping.

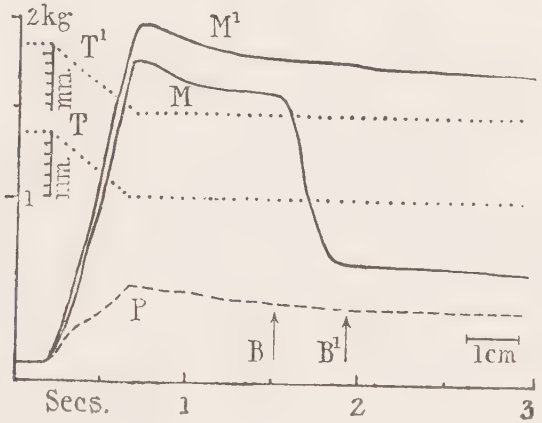

FIG. 152. Responses of quadriceps cruris to table-stretch (T) of 6 mm. before (M and M′) and after (P) severance of its nerve. During M a stretch was applied to biceps commencing approximately at the arrow B and continued for remainder of figure. During M′ a similar stretch was applied to biceps approximately at arrow B′, but after the nerve of biceps (hamstring nerve) had been cut; the stretch T′ applied to quadriceps for M′ is shown by the table record to have been slightly greater than that for M. (Liddell and Sherrington, *Proc. Roy. Soc.*, vol. 97B, p. 272, 1925.)

The motion of the limb in stepping is in a broad way divisible into two phases—the phase of flexion in which the ankle, knee and hip are lifted, carrying the foot forward above the ground; and a phase of extension in which the ankle, knee and hip are extended, bringing the foot downward to the ground and pushing the body forward from the point at which the foot touches. In the phase of flexion it is clear that the bending of the knee will stretch the extensor muscle. This will act as an adequate stimulus to the extensors and will result in their contraction. This, then, marks the commencement of the extension phase of the stretch. However, extension

of the knee joint leads to a stretching of the flexors, which in turn, will cause an inhibition of the extensors and so terminate the extensor phase of the step. The extensor muscles then, remain, as it were, "asleep" during the flexion period because of the inhibition emanating from the flexor muscles. The extensors, when they "awake" from this inhibition, find themselves stretched and so the rhythmic process continues until interrupted by voluntary effort. It will be seen how nearly the experiment shown in figure 150

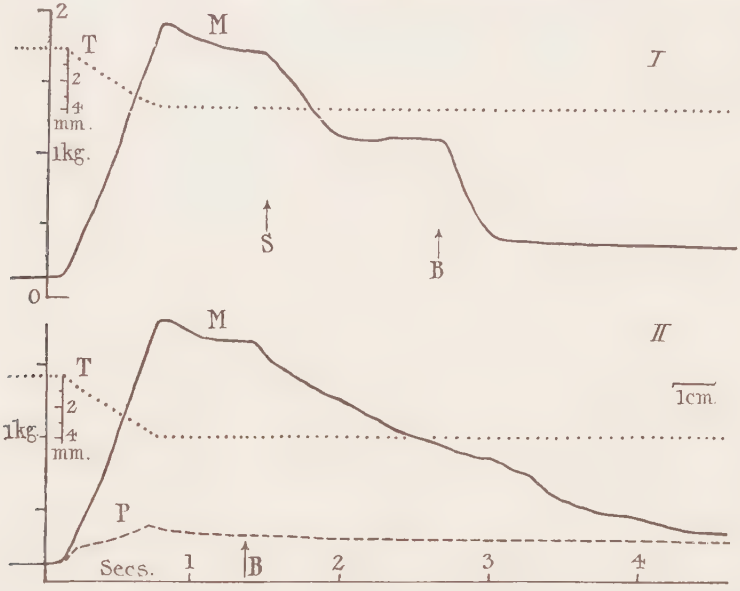

FIG. 153. (I) (II). Responses of quadriceps cruris to table-stretch (T) of 4 mm. before (M) and after (P) severance of its nerve. During the response, in I a stretch of semitendinosus beginning approximately at arrow S, followed by a stretch of biceps beginning approximately at arrow B; in II a slowly increasing stretch of biceps was applied, beginning approximately at the arrow. (Liddell and Sherrington, *Proc. Roy. Soc.*, vol. 97B, p. 276, 1925.)

repeats,—though probably with greater abruptness,—the beginning of the extensor phase of the step, that is, the figure shows clearly the condition of waking to "post-inhibitory freedom."

One may also point out that the stretch reflex is capable of combining with any pre-existing contraction which may be present in the muscle when the stretch stimulus is applied; thus in figure 155 a stretch reflex occurs "on top" of a pre-existing contralateral reflex. At the height of the two combined reflexes they are both inhibited. This is followed by a

partial recovery of the tension previously attained, the contralateral stimulus then ceases, and then the stretch stimulus is removed.

The stretch reflex, though having its origin in the stretch afferents within the muscle itself, may be modified by the higher centres of the nervous system, thus in a Magnus animal the labyrinthine and neck reflexes so carefully studied by Magnus and de Kleyn (*679*) are capable of modifying the size of the stretch reflex (*640*). For instance, when the head is turned away (*i.e., in a counter clockwise direction as viewed from in front*),

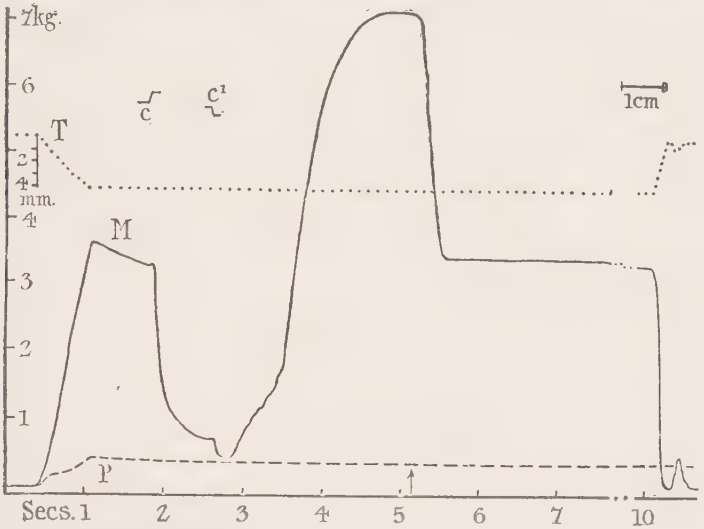

FIG. 154. Response of quadriceps cruris to table-stretch (T) of 4 mm. before (M) and after (P) severance of its nerve. During response M the ipsilateral peroneo-popliteal nerve was faradised for the period between signals C and C′, then, during the ensuant rebound contraction, a stretch of biceps was applied commencing approximately at the arrow. Later the quadriceps cruris stretch was removed by raising the table. Myograph magnified quadriceps tendon movement 116 times. (Liddell and Sherrington, *Proc. Roy. Soc.*, vol. 97B, p. 279, 1925.)

from the right hind limb used in the experiment, the stretch reflex is diminished. When turned toward the side of the experimental limb (*clockwise, i.e., when placed in the "maximal" otolith position*), the stretch reflex is augmented. This is precisely what one would anticipate from the behaviour of intact animals when the position of the head is altered (*679*).

OTHER MYOTATIC REFLEXES

It would be out of place in a work of this nature to describe categorically all of the proprioceptive reflexes which are known clinically, especially

the large number of so-called "jerk reflexes" which have been and are still of so much service in the diagnosis of central nervous lesions. These are described in many works on the tendon reflexes, especially those of Sternberg (*970*) and Hoffmann (*493*) and in clinical works (*786*, *520*). Attention may however be directed to the *distribution* of the tendon reflexes. In general they are most marked in antigravity muscles, in other words in those which show marked stretch reflexes. Yet they are not confined entirely to these, for under favourable circumstances jerks are obtainable from many flexor muscles of the body, *e.g.*, the hamstrings (Walshe, *1019*, *1020*; Magnus, *681*).

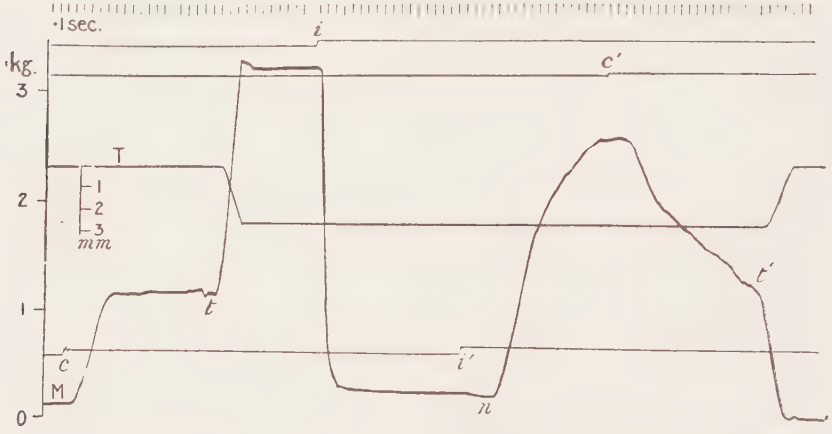

Fig. 155. Vasto-crureus. From C to C′ stimulation of contralateral afferent peroneo-popliteal nerve evoking reflex contraction. At *t* a 2.5 mm. table-stretch; at *t′* table raised to initial height relieving the residual stretched-posture. From *i* to *i′* stimulation of *ipsilateral* (*i.e.*, inhibitory) afferent nerve; at *n*, where cessation of the ipsilateral stimulus occurs, the slight ipsilateral contraction passed off through the inhibition temporarily remained. Myograph multiplying tendon-movement 62 times. Time in 0.1 second. (Liddell and Sherrington, *Proc. Roy. Soc.*, vol. 96B, p. 230, 1924.)

Myotatic reflexes of flexor muscles. Asayama (*35*) examined (in the Oxford Laboratory) the "pluck" reflex of tibialis anticus, the flexor of the ankle joint. As is well known this muscle responds with the flexor group in ordinary reflexes. Asayama found that the reflex, though short-lived, is to be obtained from tibialis both in the spinal and decerebrate condition, that the integrity of the tendon is not necessary for the elicitation of the reflex, and that the reflex disappears on severance of appropriate posterior roots, thus proving that it is not an idiomuscular phenomenon. Often the response of tibialis to a stretch may be in the nature of a short clonus. In

decerebrate preparations one occasionally observes "pluck" reflexes of the knee flexor, semitendinosus, but these reactions are somewhat inconstant and have not yet been made the subject of systematic analysis. The flexor muscles of the knee-joint never appear to show prolonged myotatic *contractions* comparable to the stretch reflex, and it is unlikely that tibialis would yield them, though this has not been adequately tested.

Flexor muscles do, however, yield a prolonged myotatic *reflex* effect, but it is in the nature of reflex inhibition of antagonistic muscles, and this we have already described.

"Crossed" myotatic reactions—Philippson's reflex. It was Philippson (*772*), who first observed that stretching the quadriceps of one side evoked contraction of the opposite quadriceps, or, as he expressed it, "forced flexion of the leg upon the thigh provokes in the opposite limb extension of the leg and foot, the thigh remaining flexed." Sherrington (*919*) has made this reflex the subject of careful examination and finds that it is best elicited in an animal lying in the supine position the opposite knee being passively flexed and the knee on the side to be stretched passively extended (so that the quadriceps will be at its shortest length). He found that in order to elicit the reflex the ipsilateral quadriceps must be stretched against tonic resistance; in other words the "lengthening reaction" must be evoked (see below, p. 432). It may be remembered that stimulation of the cut central end of any of the nerves to quadriceps will elicit contraction of the opposite quadriceps, and since this is probably due to the stimulation (among other things) of "pain" *i.e.*, nociceptive endings, it is likely that "lengthening reactions" of the ipsilateral quadriceps results similarly from stimulation of pain fibres (reflex inhibition). This will be referred to again in Chapter XVII.

RECEPTORS IN MUSCLE

It has been pointed out that the Golgi tendon organs are not necessary for the elicitation of the stretch reflex, and this is true also of certain other sensory organs in the muscle. Thus Sherrington (*886, 935*) discovered that if the cut central end of one of the four nerves supplying quadriceps is stimulated, the remaining three portions of the muscle are reflexly *inhibited;* but, if any one of the parts of the quadriceps is weakly stretched that part *contracts* reflexly. In other words, there must be in a muscle nerve, afferent fibres which cause *generalized* reflex inhibition as well as fibres which give rise to *localized* reflex contraction. Since it is known: (1) That stimulation of "pain" endings causes reflex rise of blood pressure, and that stimulation of the central end of a muscle nerve causes a similar rise of

blood pressure (*898*, p. 1012), (2) since there is no rise of blood pressure during a stretch reflex, and, (3) since pain in a muscle, as a subjective phenomenon, *i.e.*, the psychial adjunct of a nociceptive stimulus, gives rise to reflex relaxation (*935*), it is highly probable that the "pain" fibres in the muscle nerve are responsible, or are among those responsible, for the generalized inhibition occurring in quadriceps on stimulating the cut central end of one of the four nerves supplying it. However, we have little information as to how these pain endings originate morphologically in muscle. Also we must leave as problematical the function of the other nerve endings such as the Golgi tendon organs and the muscle spindles, both of which are known to be sensory. In view of the general distribution and importance of the stretch reflex, it is tempting to infer that the most numerous variety of afferent endings are those responsible for this reflex. These most certainly are the muscle-spindles. The Golgi tendon organs, the basket-endings, the tendril-terminals, the Pacinian corpuscles, etc., may also be concerned indirectly with the stretch reflex, but it seems more likely that the tendon organs at least, as Sherrington has suggested, are "tension recorders," providing sensual data for the higher centres of the nervous system (*898*). While the sensory organs occurring within the body of the muscle are more likely "length-recorders," and that these are concerned with stretch reflex. Functionally, therefore, there are at least three well-recognized varieties of afferent nerve termination in muscle and morphologically there are even more: (1) The "pain" endings giving rise to generalized reflex inhibition; (2) the muscle-spindles; (3) the Golgi tendon organs, Pacinian corpuscles, etc., which possibly supply sensual data for the higher centres of the nervous system.

The following considerations are also relevant to the function of the muscle spindles. The fact that these end-organs differ from the other muscle receptors, by being contractile, "suggests that they function in signalling active movements rather than passive" (*898*, p. 1009). It would seem probable that their adequate stimulus is the change of form produced by the intrafusal fibre, when it contracts or when its fellows contract. Until lately, however, no clear-cut evidence was on record to show that muscle proprioceptors *are* stimulated by active contraction; but the recent (1924) beautiful experiments of Forbes, Campbell and Williams (*328*) have settled the question conclusively (see below, Chapter XVII). They find that when a motor nerve is excited by a break shock, the ensuing contraction causes stimulation of the muscle proprioceptors, whose action currents can be detected in the nerve. The volleys of proprioceptive impulses thus elicited fall into several groups, which vary in number and time relations according to whether or not the muscle is permitted to shorten during activity. As we shall see, active contraction causes, among other things, reflex autogenous inhibition of the active muscle. Consequently, if the muscle spindles are stimulated only by active contraction, it would follow that they belong to the group of inhibitory proprioceptors, rather than to the "stretch-afferents," as has been suggested.

Moreover, we have now to consider the recent (April, 1926) notable discovery of Byrnes (*184*) that in paralysis agitans, an obscure locomotor disease characterized by central degenerations in the *substantia nigra* and *corpus striatum* (see *1056*), there are also present pathological lesions peripherally in the muscle spindles. It is as yet immature to decide how much light this may shed upon the function of these end-organs, but the observation is of great significance to the pathology of the disease. It may be noted in passing that knee-jerks are usually unaltered (*i.e.*, "clinically") in the Parkinsonian syndrome; consequently, if the muscle spindles are not functional in this condition, it is unlikely that they are to be associated with the "stretch-afferents." Morever, Byrnes states his belief that the muscle spindles *are* inhibitory afferents, and that when they do not function the proprioceptive centres are "released" from inhibitory control (see Ch. XXI) and Parkinsonian rigidity is the result.

Adrian and Zotterman (*19*), however, have lately recorded the response to stretch of an apparently single muscle spindle (sterno-cutaneous muscle of the frog), and it might be urged that this establishes the function of the spindle as the "stretch-afferent." But this does not follow for we have no way of deciding what the reflex effect of the impulses set up in these experiments would be: *i.e.*, whether excitation or inhibition. We shall see in Chapter XVII that severe stretch may give rise to inhibition.

The functional significance of the "pain" endings in muscle is sometimes not realized (cf. Hough, *500*). As Sherrington has said (*935*), "We must not forget that muscles can give rise to pain. Cramp, rheumatism, muscular fibrositis, and neuritis evidence this [pain] only too commonly. Even a small partial rupture of a muscle makes it a seat of pain when it contracts. In all such cases the treatment that the physician's experience enjoins is rest, that is the treatment that Nature herself seems to aim at, for she enforces it, in the last resort prescribing pain, if rest be departed from. Existence of these inhibitory afferents from muscle suggests she enjoins involuntary desistence from contraction by reflex inhibition."

The relation of the stretch reflex to muscle tonus, to the "lengthening" and "shortening reactions" and the nature of the electrical responses of muscle during the stretch reflex will be considered in the following chapters.

SUMMARY

Stretch applied to the knee extensor of a decerebrate or thalamic preparation evokes active contraction of a reflex character. The receptors for the reflex lie in the fleshy region of the muscle and it is therefore a purely proprioceptive phenomenon. The reflex may be elicited by a stretch of less than 1 per cent of the total muscle length. Slow stretches, *e.g.*, 5 mm. in 6 seconds, elicit the reflex as well as quick stretches though the size of the reflex is less with the abrupt stimulus. The latency of the reflex is of the same order as that of the knee-jerk, *i.e.*, 6 to 9σ.

The reflex is characterized by relatively complete absence of after-

discharge the reflex disappearing immediately the stretch ceases. Other things being equal, the reflex continues to increase as the stretch increases. The reflex has been divided in two periods: (1) the phasic or kinetic period, which corresponds with the mechanical ascent of the reaction and is confined roughly to the period during which the muscle is being stretched, (2) the static or postural period during which active contraction is maintained after the stretch has ceased.

The response to stretch in decerebrate preparations is intensely local, being confined to the muscle or portion of the muscle stretched. The smallest reflex unit is presumably a single stretch afferent with the surrounding group of muscle fibres which it controls.

Proof that the reaction is a reflex comes from the fact that it may be completely inhibited by an appropriate ipsilateral stimulus, and also to the fact that the reaction disappears completely when the nerve is cut.

The knee-jerk and patellar clonus appear to be fractional manifestation of the stretch reflex.

Being confined to the antigravity muscles, the stretch reflex suggests itself as an important element in the reflex coördination of postural standing, as well as of stepping.

There are at least three functionally different groups of sensory end-organ in muscle.

CHAPTER XVI

The Mechanism and Functional Significance of the Tonus of Skeletal Muscle

We have seen in the Introduction that the term "tonus" was used in Roman times by Galen in a sense not far removed from that in which the word is employed at the present day, as signifying "active posture." In the development of the physiological knowledge the word has been given a great variety of unfortunate and confusing meanings, the Galenical conception having been disregarded by the majority of writers. The modern tendency, however, has been to return once more to Galen's beliefs. We shall see that Hughes Bennett's (*69*, p. 298) much-quoted definition of tonus as "that state of slight constant tension which is the characteristic of healthy living muscle" is inadequate, since tonus is not found universally, but is distributed among various muscles in accordance with their postural functions. The establishment of this conception and the associated discovery of the importance of the proprioceptive system marks one of the great developments in modern physiology. For all of the pioneer work in this field as well as for most of the later contributions to the subject, we are indebted to the genius of Sherrington.

It was Johannes Müller (*727*) who first employed the word "tonus" as meaning a slight contractile tension characteristic of normal skeletal muscle when at rest, and he attributed this tension to the influence continually exerted upon the muscle by the nerve centres in the brain. In the early nineteenth century such investigators as Heidenhain[1] (449), Auerbach (40), Schwalbe (*854*), and Pflüger (*771*) came to disbelieve in the existence of tonus for they were unable to find evidence (in the frog) of an anticipated slight elongation of the muscle on cutting the motor nerve. Though Marshall Hall (*430*), without proof, regarded the tonus of the sphincters as a spinal reflex, it was Brondgeest (*158*) who first demonstrated experimentally that the flexor tonus of a frog's hind limb was diminished after severing appropriate posterior roots, and he attributed this to the disappearance of the "tonic reflex." The observation was soon confirmed and came to be generally accepted, but the failure to find definite elongation

[1] Heidenhain gives a most useful historical account of the early conceptions of muscle tonus.

of skeletal muscle after severing the motor nerve remained unexplained, and in 1881 Eckhard[2] (*264*) adopted the view that tonus was not necessarily present in all muscles. von Anrep (*33*), however, did find evidence of lengthening of the frog's gastrocnemius on severing the motor nerve, and observed that lengthening of the muscle occurred similarly after curare. Though Eckhard was inclined toward the view that tonus might be a reflex cutaneous in origin, Mommsen (*719*) demonstrated in 1885 that Brondgeest's experiment still holds after the hind limb has been stripped of its skin. It is surprising that this long-abandoned theory of the cutaneous origin of tonus should be again revived in recent years (*746*, *747*), especially in the light of Sherrington's (*886*, *915*, *919*) most painstaking repetition on mammals of Mommsen's experiment on the frog. As is well-known Sherrington found that the condition of heightened tonus characteristic of decerebrate rigidity disappeared completely on severing the afferent roots, but that it remained uninfluenced after section of all the cutaneous nerves to the limb. It is of course true, as Magnus (*681*) has recently emphasized, that cutaneous stimuli may modify tonic reactions (*e.g.*, the positive supporting reaction), but cutaneous nerves are in themselves quite unnecessary for the maintenance of tonus.

We may now examine the distribution of tonus in the skeletal musculature.

THE DISTRIBUTION OF TONUS AMONG SKELETAL MUSCLES

The literature of muscle tonus has been burdened in the past and is still being burdened by observations which have not taken into account the *functional significance* of tonic activity. Tonic manifestations have been sought for indiscriminately in all muscles, at all times, and not infrequently the operative procedure of the investigator has caused the very tonicity he has sought for to vanish.

Tonus is distributed in the limb musculature of vertebrates on a plan of strict coördination, but it is not confined to the musculature of the limbs, for it is present in other regions as well. It obtains, for example, in the retractor muscles of the neck, in the caudal regions (lifting the tail), in the eyelid muscles, in the masseter muscles that close the jaw, and it appears to be present in the ventral muscles of the abdominal wall. In the limbs, we find it most markedly developed in the extensor muscles, viz., vastocrureus, supraspinatus, and gastrocnemius. It is evident therefore

[2] Eckhard's series of papers (1881–1885) on the history of the experimental physiology of the nervous system are indispensable to anyone interested in the development of neurophysiology.

that the distribution of reflex tonus is such as to maintain the animal in the erect posture, in this way counteracting the effect of gravity in the animal as a whole. In muscles antagonistic to the antigravity muscles, *e.g.*, in the flexors of the hind limbs (mammals), reflex tonus is generally slight in extent or even completely absent. In Sherrington's (*927*) words (pp. 197 198):

"Reflex tonus obtains in, and is confined to, those muscles which maintain the animal in an erect attitude. That it is so may be demonstrated by setting the decerebrate preparation on its feet; it is then seen that the preparation stands. Thus this reflex tonicity, which when seen in a single isolated muscle prepared for the myograph, does not carry on the face of it any very obvious biological purpose, does carry a clear and unmistakable biological purpose when the phenomenon is followed in the musculature as a whole. *The reflex tonus is postural contraction. Decerebrate rigidity is simply reflex standing.* The reflex tonicity of the skeletal muscles of the decerebrate cat and dog is shown by its coördination, its effects, and its distribution in the musculature, to be a reflex which differs from the reflexes more commonly studied mainly in this, that the latter executes *movements* while this maintains *posture.*

Our chief problem then is to discover how in terms of what is known concerning the physiology of muscular contraction this tonicity of antigravity muscles is maintained. We know that it is a reflex and that it therefore depends upon continuous stimulation of afferent endings. The immediate problem for consideration is therefore more one concerning the motor side of the reflex arc. There have arisen in recent years two theories to account for the contractile activity of tonic muscles. One group of investigators maintains that the static features of tonicity are controlled through the sympathetic nervous system (*113*, *582*, *509*, etc.), but that phasic contraction, necessary to movement, is controlled by the somatic motor nerves. The opposed view, which in the past has been tacitly assumed by certain investigators (*774*, *781*), has recently been strengthened (*252*, *183*, *269*, *365*) and put forward as a theory. It maintains that *all* forms of contractile tension, whether static or phasic, are due to all-or-none contractions of individual muscle units under the integrative control of the somatic nervous system. We shall consider first the evidence of those who hold that tonus is controlled by the sympathetic nervous system.

ANATOMICAL EVIDENCE FOR SYMPATHETIC CONTROL OF THE TONUS OF SKELETAL MUSCLE[3]

Anatomical considerations. In the complex assemblage of mammalian skeletal muscle, several types of functional unit are to be distinguished.

[3] In preparing this action I wish to acknowledge my indebtedness to Adrian's (*5*), Cobb's (*203*) and Walshe's (*1027*) recent excellent critical reviews.

First and most important are the so-called *pale fibres*, which predominate in all quickly moving muscles. They are the thickest of the muscle units, containing a relatively small amount of sarcoplasm, and they are characterized by distinct and regularly-arranged crossed striations and indistinct longitudinal striations. The nuclei of these fibres lie at the periphery close to the inner surface of the sarcolemma and usually congregate in large numbers at the motor end-plate. It has been shown that these end-plate nuclei are ordinary muscle nuclei which in the course of development have migrated from within the fibre (*502*, *110*, *976*).

In many muscles, in addition to the pale fibres, there are present the so-called *red fibres*. These are characterized histologically by more or less irregular crossed striations and conspicuous longitudinal striations, by nuclei which are not confined to the inner surface of the sarcolemma but scattered through the whole fibre, and by the presence of a derivative of haemoglobin termed myohaematin. They are also much richer in sarcoplasm than pale muscle (Bottazzi, *132*, *133*.) Usually these fibres have a copious blood supply (*794*). Further histological distinctions are given by Sharpey-Schafer (*869*). Cobb (*203*) has pointed out, however, that there is no sharp line of distinction between the two types, as many intermediate varieties of fibre are to be found. It is therefore more satisfactory to divide muscles into a primitive type with small fibres and centrally placed nuclei, and the more highly developed type possessing less sarcoplasm, clear striations and peripherally situated nuclei.

As to the *distribution* of these primitive and more highly developed types of fibre, Grützner (*425*) has found that in man all muscles are composed of a mixture of the two types, the larger muscles tending to be evenly mixed and only the small muscles showing sufficient differentiation to permit of their definite classification as red or white muscles. For example, the *crico-arytenoideus lateralis* and the *inter-arytenoideus* he regards as purely red muscles, while the *crico-arytenoideus posticus* is a pale muscle containing but few red fibres. Roberts (*817*) and Kronecker and Stirling (*560*) regard the gastrocnemius as exclusively pale and the soleus exclusively red (cf. Paukul, *760*). But they present no evidence in the case, *e.g.*, of gastrocnemius, that red fibres are not present in small numbers. The intermediate view that all muscles of higher vertebrates are in reality a mixture in which one or other of the types may predominate is probably nearer the truth (Starling, *964*). Differences have also been recorded (Biedermann) between the homologous pectoral muscles of birds, according as they are strong fliers or merely fluttering birds such as the domestic hen, the strong fliers having red muscles, the flutters white, but no general rule of this nature has found to hold (Cobb and Fulton, *205*).

FIG. 156. Muscle spindle surrounding intrafusal muscle fibres. (Ruffini, *Journ. Physiol.*, vol. 23, p. 190, 1898.)

Muscle spindles. Sherrington showed in 1894 that the so-called "muscle spindle" is a specific sensory organ (*880*). Ruffini (*829*) had suggested the year before that it might be sensory, and the fact that it and its intrafusal fibre were found by Sherrington to be unaffected by cutting the ventral roots proved Ruffini's surmise to be correct. Now the intrafusal fibre is peculiar in having two types of nerve ending (fig. 156): a large medullated nerve taking origin in the folds of the spindle, together with a fine unmyelinated fibre. Not only are the intrafusal fibres unaffected by cutting the anterior roots, but they are likewise uninfluenced by section of the sciatic nerve itself (*880*). The spindle itself, however, degenerates after dorsal root section. The origin of the non-medullated fibres supplying the fibres spindle, however, has never been settled (see Langley, *590*), though many have speculated concerning their nature. Kulchitsky (*569*) held them to be "motor" sympathetics; Boeke (*111*) concluded that they are sensory, and Dart (*222*) that they arise from peripheral ganglion cells, but no one has traced and proved their origin, and the *function* of these unmyelinated fibres still remains a mystery.

The "intrafusal" muscle fibre within the spindle organ contains myohaematin and possesses other features in common with red fibres.

Innervation of red and white muscles. The question of the innervation of striated muscle turns largely upon the significance attached to the non-myelinated fibres accompanying the somatic nerves, and to the way in which they terminate in skeletal muscle. The somatic nerves have characteristic clearly recognizable end-organs and the only question which can be raised concerning them is as to whether two somatic motor fibres ever innervate a single muscle fibre. As we have seen in Chapter VI, the experimental evidence is strongly against the existence of plurisegmental innervation, at least in proximally situated muscles, so we may turn our attention at once to the significance of the non-myelinated endings.

It was Tschiriew (*993*) who first described non-myelinated fibres going to skeletal muscle, and he believed them to be a part of the sympathetic system. Since then the important investigations of Boeke (*108, 112*), Tello (*976*), Dusser de Barenne (*253*), Agduhr (*22*), Kulchitsky (*569*), and Kuntz and Kerper (*571*) have given strong support to Tchiriew's original inference.

The evidence on which Boeke's conclusions rested was drawn largely from degeneration experiments, but these were at first regarded as inconclusive. However, in 1919, Boeke and Dusser de Barenne (*111, 112*) performed a new series of experiments which gave convincing evidence in favour of Boeke's original contention. In these they cut the anterior and

posterior roots of the 6th to the 9th thoracic nerves (of the cat), and also extirpated the corresponding spinal ganglia in order to exclude *all* sensory

FIG. 157. Illustrations of both myelinated and non-myelinated nerves supplying individual fibres of skeletal muscle. (Boeke, *Libro en honor de Ramon y Cajal*, Madrid, p. 118, 1922.)

fibres. After allowing 30 days degeneration time, the animals were killed and appropriate intercostal muscles examined. No myelinated nerves

were found, and no sensory end-organs, but the muscles were still abundantly supplied by non-myelinated fibres with their "terminaisons en grappes" (fig. 157). These experiments appear to be clear-cut and decisive, and free from the objection raised by Langley (*591*) that sympathetic nerves supplying arterioles and capillaries have not been taken into consideration in experiments of this sort, and certainly they meet his criticism that if non-myelinated fibres could be traced back far enough they would be found to arise from myelinated fibres.

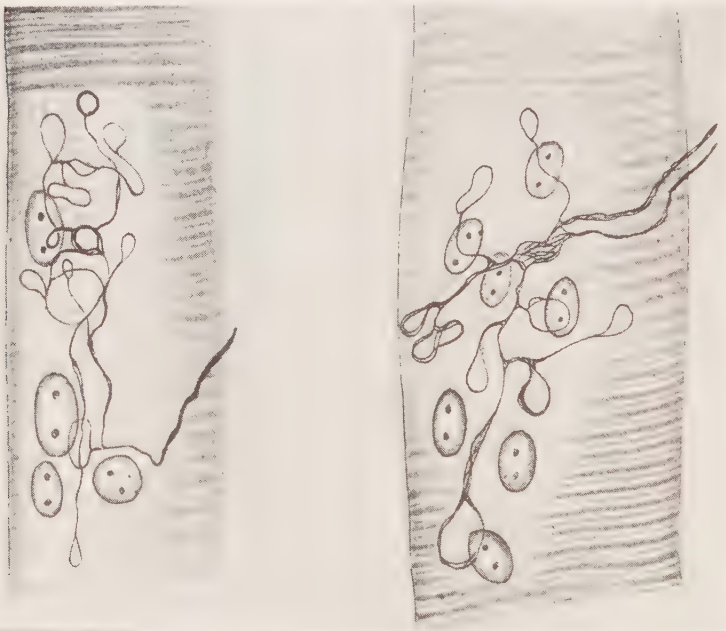

FIG. 158. The *Terminaisson en grappe* observed in intercostal muscles after degeneration of sensory and motor roots. (Boeke, *Libro en honor de Ramon y Cajal*, Madrid, p. 118.)

Since the publication of Boeke and Dusser de Barenne's paper, their observations have been extended by Agduhr (*22*) and Kuntz and Kerper (*571*, *572*) to the skeletal muscles of the upper and lower extremities (cats and dogs). Being based upon well-controlled degeneration experiments, their evidence is similarly convincing. It is, of course, always difficult to determine what proportion of muscle fibres have such endings. In Boeke's preparations of eye muscles (rabbits), these endings were observable on almost every fibre, but Bielschowsky (see Cobb, *203*) has pointed out that

they are apparently not so abundant in the appendicular musculature. However this may be, there is as yet no adequate data upon which to formulate an estimate of their incidence. But whatever their incidence may be, it is indisputable that many skeletal muscle fibres are supplied by sympathetic motor innervation (cf. Walshe, *1027*).

The question has arisen as to whether an indiviual muscle fibre may have both a somatic and a sympathetic nerve supply, and those who aver that the tonus is of sympathetic origin have been sharply divided over this question. The evidence, *pro* and *con*, has been discussed at length by Cobb (*203*) and it need not be repeated here. It is sufficient to say that Kulchitsky (*569*) and Hunter (*510*) believed that the sympathetic nerves pass to one type of fibre, small in diameter (possibly red), and somatic nerves to another type (the large pale fibres), and that a given muscle fibre is never innervated by both types of nerve. Dart (*221*), who examined Kulchitsky's material, and Boeke (*108*, *109*), on the basis of his own abundant preparations, were convinced that the two types of nerve frequently innervate a single fibre. Those who are skeptical of this conclusion (*510*, *591*) emphasize the extreme liability of subjective impressions in these exacting microscopic observations, and also point out that not infrequently the motor nerve itself bifurcates (cf. Chapter I, p. 72*n*) just before reaching its end-plate (Hunter, *510*), and that one of the bifurcations is often without any medullary sheath (*191*, *310*). However, Boeke's and Agduhr's preparations are so clear on this point, and it is so evident from even a cursory study of them that individual fibres *have* both types of innervation, that there would seem to be little virtue in discussing the matter further. Tello (*976*) and Kuntz and Kerper (*571*) have reported similar observations.

Hunter (*510*) and Elliot Smith (who prepared Hunter's lectures for publication) expressed their belief,—on the basis of Kulchitsky's histological preparations,—that red muscle fibres are innervated by the sympathetic and the white by the somatic. Light on this question has recently been provided by Garven (*385*) in his study of the innervation of various forms of striated muscle. In keeping with Grützner (*425*), he has found that two types of muscle fibre are to be distinguished in the striated muscles of the frog and that these fibres have characteristic motor nerve endings. To quote his description,

"Only two points in relation to their innervation will be dealt with. The innervation of the thin fibres is of great importance in relation to Hunter's work. A very large number of these thin fibres can be found to have endings of the Kühne type formed from branches of medullated nerves. To be perfectly certain of this somatic innervation, I searched for examples, of which Fig. 17 is one, in which a medullated nerve-fibre divides and

supplies both a thick muscle-fibre and an adjacent thin muscle-fibre; that is, the two types of muscle-fibres that are innervated from the same nerve-fibre. Numerous cases of this can be found. *No difference then exists in frog muscle in the innervation of the thin and thick muscle-fibres*, for at least a large number of the thin fibres. The other point of note in this muscle is the very extensive non-myelinated plexus of nerve-fibres which can be seen in it in well-stained specimens. Some branches of this plexus are connected with the walls of the capillaries. But I am convinced that the whole plexus is not related to blood-vessels alone, although I have as yet been unable to follow out the branches of the plexus to definite endings in the muscle-fibres or in the endomysium. Some of these thin non-myelinated fibres have a position similar to the accessory fibres, and are seen running with the myelinated fibre outside the sheath of Henle."

The degeneration experiments of Hay (*445*, *446*) show, moreover, that the red fibres of the soleus (rabbit),—the classic red muscle,—has ordinary motor innervation from the ventral somatic roots. Hence the inference that red muscle is innervated solely by the sympathetic (at least if one may generalize from soleus) is untenable. In other words, pale and red fibres cannot be distinguished on the basis of somatic and sympathetic innervation.

Hay (*445*, *446*), in his important study of the nerve supply of the red and white muscles of the rabbit, has compared the nerves of the pale-fibred semimembranosus with the nerves to the red-fibred soleus, and finds that the *number* of nerve fibres supplying the respective muscles is approximately the same, weight for weight of muscle substance; if anything, the soleus has a slightly larger number of fibres per gram of muscle than has semimembranosus. Thus, a 6.1 gram semimembranosus muscle was supplied by 1134 fibres, while a 1.3 gram soleus was supplied by 249 fibres. The average *diameter* of the nerve fibres of the pale muscle was, however, greater than the diameter of the nerve fibres to the red muscle. Analysis of Hay's figures shows that if diameter of fibre be plotted against their frequency of occurrence, two peaks occur for the nerves to pale muscle at approximately 15.5 and 12μ. The nerves to red muscle, on the other hand, have two peaks of frequency at about 12μ and at 9.5 to 10μ respectively. If, however, the anterior nerve roots are sectioned and the motor nerves thus caused to degenerate, the average diameter of the remaining (sensory) fibres from the two types of muscle becomes approximately the same: the 15μ peak disappears for the pale muscle, and the 10μ peak disappears for the red. The conclusion to be drawn from this is that whereas the afferent nerve fibres to the two types of muscle are of approximately the same size (12μ), the motor fibres differ in diameter by approximately 5μ. Four of Hay's excellent plates illustrating these observations are reproduced in figure 159. Hay's observations were unfortunately not numerous and further observations are needed to settle the precise shape of the frequency curve. The above description has been drawn up from his tabulated results.

The differing diameter of motor fibres to the red and white muscle respectively would lead us, on the basis of the Göthlin-Lapicque hypothesis (Chapter I), to infer that the excitatory properties of the nerve to soleus would differ from those of the nerves to semimembranosus or gastrocnemius. Lapicque and Legendre (*611*, *612*) have pointed out that the chronaxie of nerve fibres decreases with increasing diameter of fibre, and Göthlin (*399*, *400*) has similarly emphasized that the threshold of excitability falls with increasing

size of fibre. It is therefore of interest to find that in the mixed popliteal nerve, stimulation with gradually increasing intensity of stimulus causes the pale-fibred gastrocnemius to respond first, and only after considerable further increase does the soleus respond. The chronaxie, however, of these two muscle nerves has not yet been accurately determined.

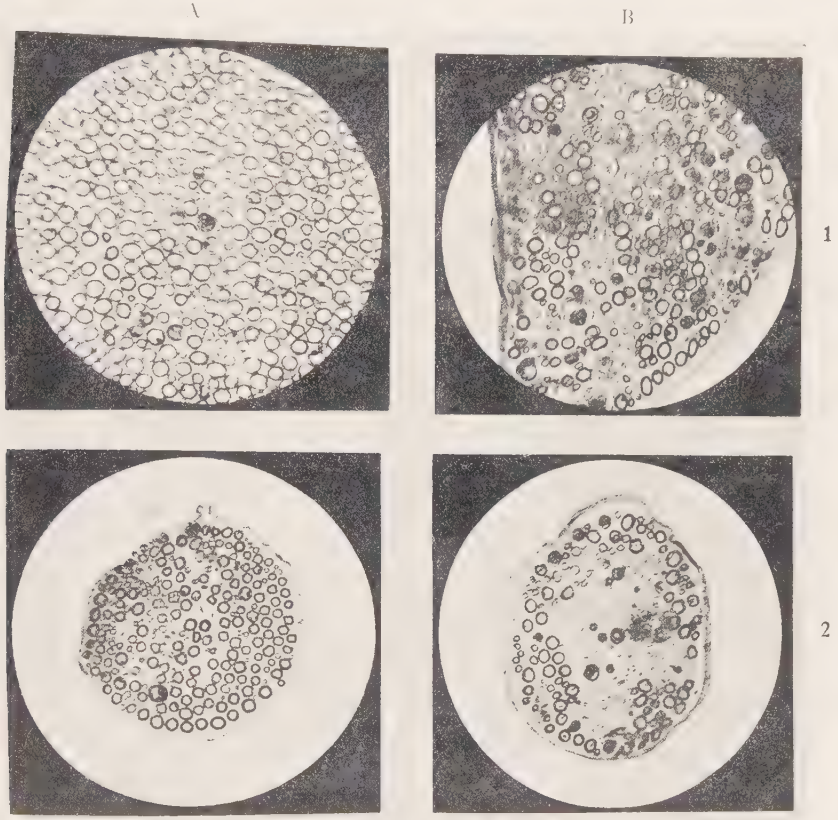

FIG. 159. *1.* Transverse sections of the nerve to the pale-fibred semimembranosus muscle of the rabbit before (A) and after (B) degeneration of the efferent fibres following section of the ventral roots.

2. Transverse section of the nerve to the red-fibred soleus of the same animal before (A) and after (B) degeneration of the efferent fibres. Note that the average size of the large medullated fibres is approximately the same in the two muscles after exclusion of the efferent fibres. (Hay, *Liverpool Med.-Chirurg. Journ.*, vol. 41, p. 435, 1901.)

A comparison of the contraction of red and pale fibres. (See above, Chapter IV.) Ranvier (*793*) and Grützner (*425*) showed more than 30 years ago that the primitive red muscles contract more slowly than white fibres, and after a longer latency, they also found as a necessary consequence that

fused tetani are produced at a lower rate of stimulation in red muscles than in white. Hay (*446*) and Roberts (*817*) confirmed these observations, and Hay pointed out that red muscles withstand cessation of the circulation for greater periods than do white (fig. 160). Recently Cobb and Fulton (*205*) have examined the electrical and the mechanical responses of red muscle with an apparatus similar to that described in the Appendix, and have confirmed the observations of the earlier investigators (see Chapter IV). They found in addition that the isometric twitch of red muscle is characterized by an "angle" similar to that of white muscle and that the

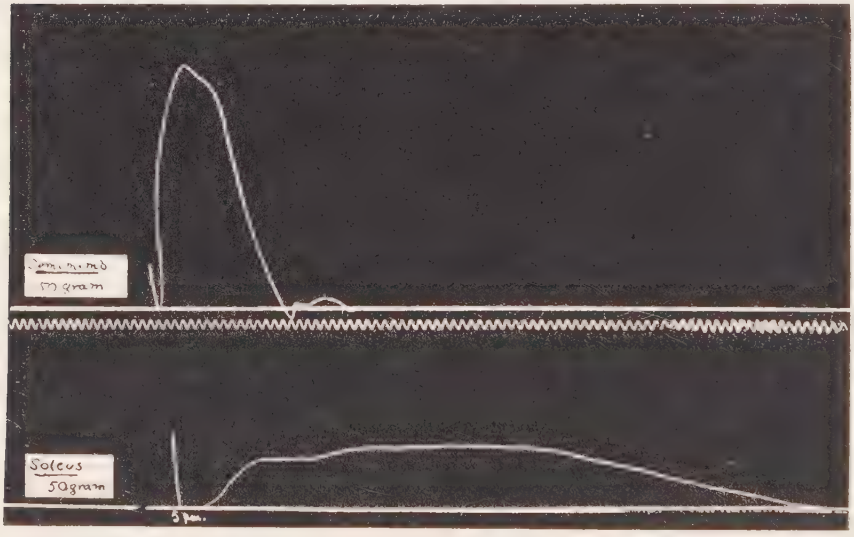

FIG. 160. Tracings of the twitch contraction of the rabbit's semi-membranosus and the soleus. Note differing durations. Time, 0.01 second. (Hay, *Liverpool Med.-Chirurg. Journ.*, vol. 41, p. 433, 1901.)

duration of the soleus twitch of a cat (measured to the angle) is approximately 3 times greater than the duration of a corresponding twitch of a cat's gastrocnemius. A noteworthy characteristic also of the responses of red muscle is the prolonged plateau (figs. 48, Chapter IV, and 160). The electrical responses were found also to be about 4 times longer in duration than the electrical response of the gastrocnemius (cf. Adrian, *12*). This provides another example of the parallelism between electrical response and the mechanical activity of skeletal muscle. It is evident from these observations that the contractile mechanism of red muscle, though slower, is in every way similar to that of white muscle.

The question of sarcoplasmic contractility. The belief that the sarcoplasm, as distinguished from the sarcostyles, is an actively contractile part of a muscle fibre was urged originally by Bottazzi (*131, 132*) in 1898. This author drew attention to the suggestive relation between the duration of a single contractile response of a given type of muscle and its sarcoplasmic content. Smooth muscles, which contain very large amounts of sarcoplasm, contract slowly and remain contracted for relatively long periods of time, in response to an apparently single stimulus. Among skeletal muscles one finds that the red-fibred variety is richer in sarcoplasm than the pale-fibred, and that the duration of the twitch is very much longer in this type than in the pale-fibred muscle. This led Bottazzi to promulgate the interesting hypothesis that phasic rapid contraction is due to the sarcostyles, while the maintenance of the tension thus developed is facilitated by the sarcoplasm, that in any one fibre two different contractile mechanisms exist, one innervated by the somatic nerves and another controlled by a neural mechanism as yet imperfectly understood.

We have seen in Chapter IV that the early evidence for Bottazzi's theory was drawn from the so-called "tonus waves" observed in the tortoise auricle, Bottazzi believing originally that the rapid rhythmic responses were due to the sarcostyles while the slower undulations were due to the sarcoplasm. A few years after this, Rosenzweig (*821*) demonstrated the existence in turtle heart of extensive bands of smooth muscle fibres in addition to the ordinary cardiac muscle fibres, and suggested that the "tonus waves" were due to contraction of this smooth muscle sheet. Bottazzi (*133*), undisturbed by this discovery, pointed out that according to his theory smooth muscle *is* the tonic muscle par excellence. Thus he says (p. 176), "Io ho sempre affermato nelle mie pubblicazioni che il tessuto muscolare liscio è il tessuto del tono per eccellenza; e che la funzione del tono digrada da quel tessuto al tessuto miocardico, da questo ai muscoli striati rossi, per ridursi a un minimo nei muscoli striati bianchi. Ora i muscoli lisci sono i più ricchi in sarcoplasma, e in riguardo alla ricchezza in sarcoplasma nello stesso ordine decrescente seguono gli elementi contrattili proprii del miocardio, i muscoli striati rossi, i muscoli striati bianchi." Bottazzi maintained, therefore, that Rosenzweig's observation, which he incidentally confirmed, in no way detracted from the validity of his original conception. He remarks (p. 178), "Ciò chè più importa però è che esistono altre strutture muscolari, nelle quali da nessuno è ammessa la coesistenza di elementi di natura diversa, e pure eseguiscono o possono essere indotte ad eseguire due ordini di contrazioni distinte; alcune più rapide, altre più lente, le prime delle quali possono essere attribuite alle fibrille striate, le seconde al sarcoplasma." He considered the possibility that tonic contraction may be in all cases brought about by fibres of different physiological characteristics from the rapidly contracting fibres as in the tortoise heart, but pointed out that there is no adequate evidence for the existence of such elements in skeletal muscle, and he therefore retained his theory in its original form in order to account for the tonus of skeletal muscle (*133*, p. 179). Bottazzi's view has been adopted by Ioteyko (*513*), Roberts (*817*), and Pereira (*764, 765*), more or less as it was first set forth. However, Boeke (*108–112*), de Boer (*113*), Langelaan (*579, 581, 582*) and others (*22, 314, 335*), who adopted the conception, have modified it,

attributing to the sympathetic system the control of the sarcoplasm. But Bottazzi (*135*) himself vigorously dissents from this conclusion on the grounds of his negative results obtained on stimulation of the sympathetic fibres passing to the diaphragm (the somatic fibres having been allowed to degenerate). The evidence which has been urged by Boeke (*109*, *110*) and others in favour of the view that sympathetic fibres innervate the sarcoplasm, is based upon the intimate histological association of the nerve endings with the sarcoplasmic regions of the muscle. Thus Boeke notes (*110*, p. 19): "Now these sympathetic nerve-endings have the same hypolemmal position as the common motor-endings, and indeed are often found embedded in the same mass of granular sarcoplasma. Moreover it is certainly of interest that surrounding the end-loops and end-nets of these sympathetic nerve-endings there may be distinguished exactly the same regular protoplasmic network as was described for the motor-endings. And, indeed, where these sympathetic endings were found embedded in the sarcoplasm of the motor-ending itself, the same periterminal network was seen surrounding them both." Boeke, in his reserved and thoughtful papers, is conscious of the danger of drawing conclusions as to function from structural appearances, and many other workers (*365*, *591*, *1027*, *203*, *5*, *59*, *332*) find it difficult to accept the belief of de Boer and Langelaan that the sarcoplasm *is* a sympathetically innervated functional unit of skeletal muscle fibres, since the only available "direct" evidence is that drawn from histological structure.

Bottazzi (*131*, *132*) drew attention in his early communications to a similarity between the contraction curve of skeletal muscle when poisoned by veratrin, and the curves of contraction of smooth muscle and of denervated skeletal muscle. He suggested in view of this that veratrin stimulates the sarcoplasm separately from the contractile elements, and that the lethargic contractions of denervated muscle are sarcoplasmic in origin since the sarcostyles have largely degenerated. This view was also adopted in 1916 by Roberts (*817*) to account for his observations on denervated muscles. The hypothesis carries with it the tacit assumption that sarcoplasmic contraction is effected with great efficiency, *i.e.*, without extensive heat-production or lactic acid liberation, as in certain invertebrate "fixing" muscles. Hartree and Hill (*441a*), however, have shown that in veratrin contraction (frog) there is a prolonged heat liberation, which, as in a tetanus, is proportional to the force maintained. Lactic acid is produced and there is therefore no adequate ground for believing that a veratrin contracture is different from a tetanic contraction. Gasser and Dale (*388*), moreover, have found that lactic acid is produced in denervated muscle when responding to direct stimuli. Bottazzi's conception of sarcoplasmic contractility based upon veratrin and denervated muscle curves, is therefore excluded.

Since veratrin causes a generalized diminution in the chronaxie of muscle fibres (*608*), it follows that this alkaloid must have a direct action upon the muscle substance, especially since veratrin effects have been observed in the response of an individual muscle fibre (Pratt). This is also borne out by the fact that it produces its characteristic effect upon a denervated muscle (*132*, *576*). Wible (*1043*) has argued that veratrin acts upon nerve rather than muscle, and states in support of this contention that the "lower end" of sartorius in his experience was seldom affected by veratrin, while the upper end was. He says that "the upper part of this muscle contains nerve fibres while the lower part does not," which is erroneous. Therefore his evidence in this case points rather to a direct muscular effect than to an effect upon the nerve.

More recent experimental evidence urged as favouring the conception of sarcoplasmic contractility is based upon the fact that in *all muscles* a

reversible heat flocculation of sarcoplasmic proteins occurs at 45° (warm contracture), while at 50° to 52° warm contracture passes into irreversible heat rigor. Warm contracture, Bottazzi (*134*, *136*) believes comparable to tonic contraction; he compares the sarcoplasm of muscle to the protoplasm of unicellular organisms, adding that "it would be strange if embryonic myoblastic protoplasm should have parted with its original contractility after having engendered a new contractile structure, the fibril."

It must be noted that there is no direct evidence for the "sarcoplasmic" theory, and that it is founded largely upon inferences and analogies. Consequently it is difficult to pass final judgment upon it; especially is this true when we realize that the hypothesis appears to be unnecessary to account for the phenomenon which it was devised to explain, namely, the maintenance of posture of skeletal muscle (*365*).

EXPERIMENTAL EVIDENCE CONCERNING THE SYMPATHETIC CONTROL OVER MUSCLE TONE

The evidence in favour of the participation of the sympathetic system in the control of muscular activity rests chiefly upon the results observed following degeneration of the sympathetic nerves. The attention of physiologists was directed to the possibility of sympathetic influence by the publication in 1911 of Boeke's (*108*) important paper on the accessory terminations in skeletal muscle, and de Boer's monograph (*113*) first brought the question to experimental test. He claimed that the cutting of the rami communicantes of the abdominal sympathetic of frog caused a diminution of tone in the corresponding leg muscle. And he observed similarly that extirpation of the abdominal sympathetic chain in cats caused a corresponding diminution in tone and an exaggeration of the tendon reflexes. These observations were followed by a large number of attempts on the part of other investigators to corroborate or to criticize de Boer's conclusions. They have been supported by Langelaan (*581*), Ken Kuré (*545*) and by Maumary (*695*) and questioned by many others (*208*, *209*, *684*, *833*, *197*, *570*, *253*, *732*, *537*, *331*, *488*). Certain authors (*657*, *836*) obtained equivocal results. Recently Wastl (*1029*), who worked under the late Professor Langley, concluded that stimulation of the sympathetic in mammals fails to affect the muscle activity, save when it produces marked vaso-constriction, in which case it *accelerates* the onset of fatigue to ordinary motor stimulation. This author concluded from her experiments that the sympathetic system does not affect the functional activity of striated muscle of either frogs or mammals apart from its influence over the circulatory condition of the muscle. Mansfield (*684*) has also emphasized that circulatory

changes following upon sympathetic extirpative may be in large measure responsible for the observed sequelae.

The observations of the late Professor John Irvine Hunter (*509*, *510*) whose untimely death will ever be regretted among physiologists, added a new stimulus to the controversy. The starting point of his observations was a belief in Langelaan's contention that tonus may be divided into "plastic" and "contractile" phases. Langelaan (*580*, *581*) had urged that muscle plasticity was due to a special type of fixing mechanism which was capable of maintaining a muscle at any necessary physiological length without a great expenditure of energy. This supposed power of fixation has been compared by many investigators with the condition obtaining in the so-called adductor muscles of *Pecten* (Bayliss, *59*, Chapter XVIII). This muscle, common to the bivalve molluscs, has a remarkable power of developing great resistance to a stretching force without apparently being able of itself to shorten. Langelaan (*582*) believes "contractile tonus" attributable to the ordinary contraction of muscle fibres produced by somatic stimulation, the "plastic tonus" being due to the sympathetic. This then is the basis of Hunter's theory. Hunter further elaborates the view on the assumption (1) of the presence in skeletal musculature of red and pale fibres, the red being responsible for fixation and the pale for "contractile tonus," and (2) that pale fibres are innervated by somatic motor nerves and red fibres by sympathetic nerves. It is evident at the very outset, that the second assumption is incorrect for, as Hay (*445*, *446*) has observed, ordinary somatic nerve fibres form the motor supply of the classic red muscle, the soleus. There is, however, the observation of Kulchitsky (*569*) that nonmyelinated fibres are often seen to supply muscle fibres of small diameter (fig. 161). But Kulchitsky himself was careful not to infer that the small muscle fibres so supplied were necessarily red. According to Hunter's first assumption red muscle fibres only "*fix*" and are not capable of contractile function. But this is clearly not in keeping with the known property of red muscles, namely, that they do contract, though slowly (fig. 160). It may be urged in favour of Hunter that the apparent contraction of red muscles is due to the admixture of white fibres within them, but if this were true then the contraction of the red muscle should have the same mechanical characteristics, especially the same duration, as the contraction of a white muscle, but again this is clearly not the case. It is evident, therefore, that both of the initial assumptions of the Hunter-Elliot Smith theory are out of harmony with accepted fact. From information given to me by Dr. Cobb, it is clear that Professor Hunter was aware of both these objections before his death, and

had he lived he would undoubtedly have continued his investigations and harmonized the discrepancies.[4]

It does not follow from this, however, that the evidence which Hunter has adduced in support of his theory is without value. On the contrary, his exceptionally skilful experiments have disclosed many new facts, and the numerous original researches which they have stimulated in various parts

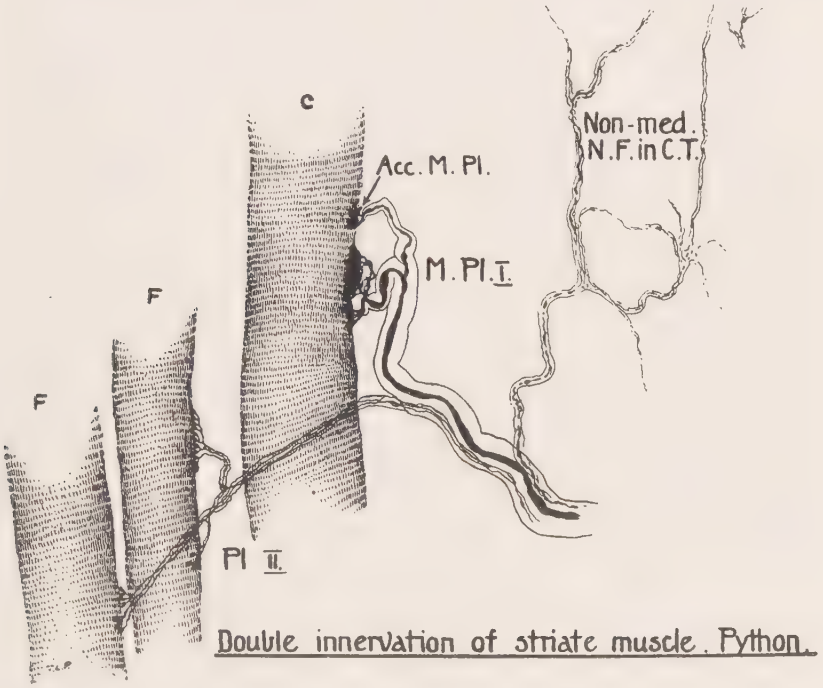

FIG. 161. Nerve endings in the muscle of python. Two fine fibres, *F*, are shown with their sympathetic endings, and a coarse fibre, *C*, with its motor end-plate, and nearby an ultraterminal ending (called "accessory motor plate" in this figure). The irregular plexus-like course of the sympathetic nerve is well shown. (Kulchitsky, *Journ. Anat.*, vol. 58, p. 152, 1924.)

of the world bear ample evidence of their usefulness. He and Royle (*508*, *828*) have performed a large series of experiments, which divide

[4] Professor Elliot Smith writes (*203*, p. 532): "In his published statements Hunter deliberately refrained from identifying the slender and coarse fibres with red and white muscle. For this suggestion about red and white muscle in the lectures (*510*) I am responsible."

themselves into three groups: (1) those on normal, spinal and decerebrate goats; (2) experiments on birds; and (3) operations on man. We will consider first the observations on goats.

In a number of goats the spinal cord was cut and at the same time, after a period of several days, the abdominal sympathetic chain was removed from one side. They observed that the leg on the sympathectomized side became somewhat flaccid, whereas the other appeared to retain its tonus. In another series of goats, the abdominal sympathetic was removed from one side and the animals were permitted the recover and after a period varying from 14 to 73 days the animals were decerebrated. The characteristic features of decerebrate rigidity appeared as usual in all four limbs but when the animal was rolled on to its back the sympathectomized limb soon fell from full extension to a somewhat abducted flexion. They claim moreover that when this leg was examined for the lengthening and shortening reactions of decerebrate rigidity they were found completely absent. When examined myographically the knee-jerk of the two hind limbs exhibited these important differences: on the operated side the knee-jerk was briefer and possessed of less "after-discharge" than the normal knee-jerk.

The experiments on birds (the domestic fowl and sea-gulls) consisted of cutting the sympathetic trunk just above the first thoracic which, owing to the anatomical arrangement of the sympathetic system in birds, serves to remove the sympathetic supply of the whole wing. After such an operation the wing on the operated side is somewhat drooped and becomes readily fatigued when the bird attempts to fly. This was beautifully illustrated by showing the flight of these birds through short distances; they tended always to circle, owing to the weakness of one wing, and at the end of a flight of a hundred metres showed marked dyspnoea and the drooping of the wing became very noticeable. This observation has been corroborated by Kuntz and Kerper (*574*). In a second series of birds the posterior roots of the four lower cervical segments were cut. After the operation the wing drooped instead of taking up its usual position, but when passively moved it appeared to remain in its new position, and this Hunter argued was evidence that the lengthening and shortening reaction was still present (cf. Walshe, *1027*). This he attributed to the fact that the sympathetics had not been cut.

With the exception of the inferences regarding the presence or absence of the lengthening and shortening reactions there can be little doubt as to the accuracy of Hunter's observations on goats and birds, though his goat experiments were not numerous; but differences of opinion have arisen

as to their interpretation. We have already seen that the assumptions regarding the nature of the innervation of red muscles and their absence of contractile activity are untrue; moreover, Cobb (*203*), among others (Forbes, *212*), has pointed out the complete inadequacy of Langelaan's (*582*) separation of tonus into contractile and plastic phases. Another weakness is the interval which must elapse after operation before the disappearance of plastic tonus. Hunter admitted that if animals were decerebrated several hours after removal of the abdominal sympathetic the tonus of the muscle on the operated side may be in every way normal, and he stated that the effects of sympathectomy are only fully seen after sufficient time has been allowed for complete degeneration of the sympathetic fibres. Now all other forms of reflex activity disappear immediately any one of the nerve channels in the reflex arc are severed. This suggests that the effects produced by cutting the sympathetics are explicable on grounds other than those suggested by Hunter. The altered blood supply (Mansfield, *684*), for instance, affects the nutrition of the muscle which would inevitably influence the sensitivity of the afferent nerve endings and in this way modify proprioceptive control. With reference to the operation on human patients, Bailey (*46*) has remarked: "The operation and the theory on which it is based will stand or fall on the immediate reduction of plastic tone following the operation. . . . . I say *immediate* reduction of plastic tone, since plastic tone is a reflex phenomenon. That the patient does or does not have better motor function six days or six weeks or six months later is entirely beyond the point and must be explained by extraneous factors." In Hunter's papers there is, moreover, no satisfying evidence that the presence or absence of the "lengthening" and "shortening reactions" was determined with the necessary precautions of careful denervation of all extraneous muscles and complete isolation of the muscle to be examined (see Chapter XVII). The lengthening and shortening reaction, though often visible to the naked eye, can only be proved absent by careful myographic investigation. In the case of the wings of birds whose posterior roots had been cut, the observations are indeed suggestive, especially as repeated in the hands of Kuntz and Kerper (*574*), but one wishes further evidence from the study of isolated muscles and also control experiments showing that all of the muscles influencing the flexion of the limb *are* actually deafferented by severance of the lower four cervical roots. Moreover, there is as yet no convincing evidence that the deafferented bird's wing loses its alleged sympathetically-produced "plasticity" when the sympathetic roots are subsequently severed.

At the present time it is impossible to draw satisfactory conclusions from

Royle's (*828*) surgical rami-sections (see fig. 162) in human cases of spastic paralysis, for the results, especially in the hands of others, are conflicting and many investigators are agreed that too many modifying factors are involved to admit of clear inferences (*212, 537*).

Within the last two years numerous observations upon the relation of the sympathetic to tonic activity have been published. Kuntz and Kerper (*572, 573, 574*), for instance, have confirmed on dogs Hunter's observations on goats.

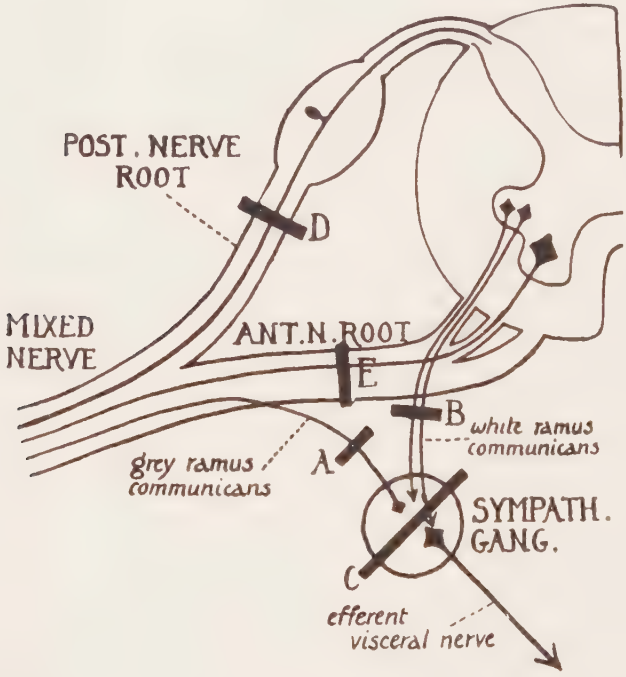

FIG. 162. Diagram of the essential sympathetic connections of the cord and nerve roots. The letters indicate the possible loci of operative lesions: A, the "rami-section" of Royle. B, cutting the preganglionic fibre. C, evulsion of the ganglion of the sympathetic chain. D, deafferentation. E, section of the motor fibres leaving the sympathetic supply intact. (J. I. Hunter, *Brit. Med. Journ.*, i, p. 200, 1925.)

Kuntz and Kerper (*574*) report an interesting series of experiments in which the tonus existing in the quadriceps muscle of intact cats and dogs was measured before and shortly after unilateral lumbar sympathectomy. Their method consisted in measuring the resistance encountered as the knee-joint is gradually flexed from complete extension through a considerable angle. Owing to voluntary activity the animals were usually slightly anaesthetized, but this circumstance did not, according to these authors,

vitiate their results, since, in docile animals which remained quiet, the same results were obtained without anaesthesia. They found that on the normal side the resistance encountered is large during flexion through 20° to 30° (away from the perpendicular), and that the resistance then rapidly diminished as the passive manipulation was carried still further. On the sympathectomized side, however, the initial resistance was much less marked; in other words, when the angle of flexion (ordinate) is plotted against T, the "tonus" (or resistance), the curve of the sympathectomized muscle rises rapidly and in some experiments was almost rectilinear, while on the normal side there was a more or less prolonged initial upward concavity. Kuntz and Kerper infer that the initial resistance of normal muscle is an expression of the "Bremsung," or brake phenomenon, discussed by Spiegel, and that this is absent after sympathectomy. Adopting Langelaan's theory of dual function, they conclude that the brake phenomenon must be due to the "plastic" element of tonus and that it is this which is abolished by sympathectomy, thus agreeing with Hunter. The objections to such a view are several. In addition to those already mentioned in discussing Hunter's theory, the following may be noted: (1) Experimental analysis of tonic reactions in the intact animal, in which various extraneous reflex factors cannot be excluded, are unreliable. (2) The "active" muscles not being isolated by complete denervation of the surrounding muscular and cutaneous structures, especially of the antagonistic muscles, renders difficult and uncertain the interpretation of their responses. These two points, however, do not account for the observed differences after sympathectomy. (3) The possibility of the differences of Kuntz and Kerper being due to secondary circulatory changes, was not excluded (cf. Hinsey and Ranson, *488*). (4) The "brake" phenomenon which they discuss can be little other than a manifestation of the stretch reflex, since it (the "brake" phenomenon) was elicited by extension of an antigravity muscle. The stretch reflex is a proprioceptive reaction effected through somatic motor nerves (Chapter XV). In unpublished experiments, Cobb, Liddell, and the author observed that the stretch reflex of the isolated quadriceps of decerebrate cats was not perceptibly altered one hour and a half after lumbar sympathectomy. (5) If a suggested explanation is not out of place, I would urge that sympathectomy in altering the blood supply modifies the responses of the proprioceptive endings within the muscle. Any factor, for instance, which leads to swelling and oedema would cause pain endings to be more readily stimulated (Chapter XVII) and this would in itself lead to reflex diminution of myotatic reflexes. Other factors will be considered when discussing Orbeli's work.

Kanavel, Pollock and Davis (*537*, *538*, *776*), in addition, operated on 16 cats and 12 human beings and found, even after long intervals, sufficient degeneration of the sympathetic chain that the quality of maintenance of tonus could not be distinguished on the operated side from that of the normal, and similar results were obtained by Newton (*732*) on rabbits, and by Forbes and his collaborators (*332*) on cats. The report of a recent clinical discussion of sympathectomy held at the Royal Society of Medicine, in which Drs. Adrian, Beattie, Bramwell, Walshe and others participated, has recently appeared in the Lancet (February 20, 1926, p. 395), and the consensus of opinion was in harmony with that of Kanavel, Pollock and Davis. A similar discussion leading to substantially the same conclusions was lately held at the meeting of the American Medical Association.

The details of the discussion have been reported in full in their Journal of June 19, 1926 (vol. 86, pp. 1886–1890; see *332* and *776*).

A large number of investigations have been reported recording negative results after administration of sympathomimetic drugs. Thus, for instance, Wastl (*1029*) and Huggett and Mellanby (*505*) failed to find any alteration of tonic activity after injections of adrenalin or atropine, while the latter authors observed complete flaccidity of all muscles after curare (cf. von Anrep, *33*; Porter, *778a*).

The evidence for parasympathetic control over muscle tonus. Within the past few years a group of investigators led by E. Frank (*335–339*) and his collaborators and by Ranson (*791, 792*), have urged that muscle tonus is under the control of the parasympathetic system (as distinguished from the pure sympathetic outflow). It will be recalled that the parasympathetic nervous system is characterized anatomically by peripherally situated ganglion cells, as was first emphasized by Gaskell. In the case of skeletal muscle of higher animals direct evidence of peripheral ganglion cells is lacking, but as Dart (*221*) has pointed out, they have in most cases not been adequately sought for; moreover, in the muscles of Python, Dart has found peripheral ganglion cells in connection with non-medullated fibres which he believes to be of (para ?) sympathetic origin. No adequate proof, however, is afforded that these fibres actually come from the (para) sympathetic system. Ranson, on the other hand, has pointed out that the cell bodies of the sensory fibres in the posterior roots (some of which cause antidromic vaso-dilatation) are in synaptic connection with non-medullated fibres of unknown origin. Frank regards the non-medullated fibres as the pre-ganglionic elements and the antidromic posterior root fibres as comparable to post-ganglionic elements of the parasympathetic system (cf. *238*).

Frank finds that certain drug effects are in harmony with a parasympathetic conception of tonic control (*335, 338*). He points out, for instance, that after degeneration of the hypoglossal nerve (conveying motor fibres) in dogs, injection of small amounts of acetyl choline will produce "tonic" contraction in the paralyzed half of the tongue, and he infers that choline and the innervation responsible for tonic manifestations act upon the same mechanism. All drugs which paralyze the parasympathetic system, such as scopolamine, inhibit the action of choline. Similarly, after degeneration of motor fibres following section of the lumbar and sacral anterior roots, acetyl choline produces tonic contraction of the paralyzed limb muscles. The same phenomenon was observed after sectioning the peripheral nerve. These observations are correlated by Frank with an early experiment of Sherrington (*880*).

Sherrington observed that 42 days after section of the anterior and posterior root supply of the sciatic nerve, faradic stimulation of the degenerated nerve trunk, if sufficiently intense, "gives slow, feeble, but steady dorsi-flexion of the ankle and sometimes extension of the toes; the movement may continue 5 seconds after cessation of application of the current and then the joints slowly return to their previous position" (*880*, p. 253). Since the motor nerves in his experiment were completely degenerated, as proved by histological examination, the effect must be dependent in some way upon the integrity of the sensory fibres from the posterior root (whose ganglia were still intact). The phenomenon did *not* occur if the posterior root ganglia were excluded and the sensory fibres thus permitted to degenerate, and Sherrington suggested that the movement might be attributed to a 'pseudo-motor reaction,' for which the undegenerated intrafusal fibres

were responsible. In 1918 these observations were investigated in detail by van Rynberk (*832*) and corroborated. van Rynberk noted that the slow movement of the ankle joint could not be elicited by stimulation of appropriate sympathetic rami. This accordingly does not favour the inference that the phenomenon depends upon sympathetic or parasympathetic control. Frank and his collaborators observed that following anterior root degeneration the Sherrington-van Rynberk phenomenon could be produced by acetyl choline as well as by nerve stimulation, and they believe that this gives added support to their inference concerning the parasympathetic control over muscle tonus. Gasser and Dale (*388*) attacked the pharmacological aspects of the problem with a view to discovering the nature of the contractile mechanism responsible for movement of the ankle joint in the degenerated muscle, and they substantially confirmed the observations of Sherrington and van Rynberk on the effect of stimulation, and of Frank and his coworkers on the drug effect. They made the added contribution that the slow movement of the muscle depends for its existence upon a lactic-acid mechanism. After stimulating the degenerated muscle they found clear-cut evidence of a rise in the lactic-acid concentration within the muscle substance. Therefore, whatever may be the neural control in this experiment, the contractile mechanism appears to be that with which we are familiar in other forms of striated muscle and thus lends no support for the belief in a special tonic mechanism within skeletal muscle. Gasser and Dale very carefully avoid any possible inferences as to the application of these observations to the broader problem of muscle tonus. Several points, however, are clear. In the first place, the acetyl choline effect is produced in the absence of the posterior root ganglion cells; in other words, in the absence of what Frank looks upon as the post-ganglionic fibres. Its seat of action must therefore be peripheral, and as there is no morphological evidence of peripheral ganglion cells we are justified in assuming that it acts either upon a hypothetical junctional tissue or directly upon the muscle. The fact that the drug effects are seen only in degenerated, and probably therefore abnormal muscle, makes one hesitate in accepting it as evidence of normal parasympathetic control over muscle tonus.

The observations of Ranson (*791*), on the other hand, are of a different nature. In a decerebrate preparation he has isolated the posterior root ganglia which supply the extensor muscle. On application of nicotine solutions to the ganglia he finds that decerebrate rigidity disappears, and in view of the classical property attributed to nicotine of interrupting synapses, he suggests that decerebrate rigidity therefore depends upon the integrity of synaptic connections within the posterior root ganglia. Stated more specifically, he believes that nicotine severs the connection between the pre- and the post-ganglionic fibres. The other property of nicotine, namely, that it stimulates before it paralyzes, is not sufficiently emphasized. In view of the fact that the nociceptive afferents which pass into the posterior roots have the power of inhibiting decerebrate rigidity, it is possible that stimulation by the nicotine is responsible for the diminution of tonus in Ranson's experiments, for it is known that excitation of any of the lumbar or sacral posterior roots of a decerebrate preparation will produce reflex inhibition of the rigidity (*344, 910, 925*). Ranson states that the application of nicotine does not interfere with sensory conduction since the extensor thrust can be elicited after the ganglion cells have been soaked with nicotine (0.04 per cent). Inasmuch, however, as the afferent roots responsible for the conduction to the cord of the impulses for the extensor thrust are not those responsible for the maintenance of tonus within the muscle (*888*), this observation cannot be regarded as convincing. Ranson accepts the Langelaan hypothesis of the separate existence of contractile and plastic tonus and assumes that his nicotine experiments

abolish plastic tonus. We have already seen that the separation of tonus into contractile and plastic components is without experimental justification, and this together with the possible stimulating effect of nicotine makes it apparent that the conclusions drawn from these experiments are open to alternative interpretations. This leaves us, however, without a clue as to the function of the synapses around the posterior root ganglia. That they are concerned in maintenance of tonus, we regard as unproved. No one has demonstrated that they are not concerned in antidromic vasomotor control. Moreover, the view that the posterior root vaso-dilator fibres are comparable to the post-ganglionic fibres of the parasympathetic system is most illuminating, for it makes possible the useful generalization that the sympathetic system controls vaso-constriction, while the parasympathetic system (*e.g.*, *nervi erigentes* and *chorda tympani*) causes vaso-dilatation when stimulated.

In a more recent communication, Ranson (*792*) has made the following statement: "If the long dorsal roots [cat] of the lower lumbar and sacral nerves of one side are cut close to the cord, atonia *seldom* develops. The deafferented muscles become markedly hypertonic and remain so for months. Atonia occurred regularly in our experiments only when the spinal ganglia were damaged." It is not stated which roots were cut, and the result, moreover, is contrary to the experience of numerous competent observers, who, by the intradural method, have cut posterior roots without exposing the root ganglia, and who have unanimously agreed that this operation abolishes forever the postural contraction normally derived from proprioceptive nerves of the affected muscles. The observation is contained in a preliminary note and cannot, therefore, be given full consideration without knowledge of the control observations, and other confirmatory evidence.

METABOLISM OF TONIC MUSCLES

The observations of Parnas (*753*, *754*) showed quite conclusively that the adductor muscles of *Pecten* consume a vanishingly small amount of oxygen when resisting severe tensile forces. Bayliss has compared this ability to withstand great stress with a negligible metabolic turn-over, to a catch mechanism (*59*, Chapter XVIII), but similar mechanisms have never been demonstrated for skeletal muscle. Though it was at one time believed that the oxygen consumption of mammalian muscle in the decerebrate condition was also negligible (*816*), it has recently been shown by Dusser de Barenne and Burger (*260*) that the O_2 consumption is 25 per cent higher in decerebrate rigidity than in the same animal immediately after section of the chief motor nerves to its muscles (fig. 163). These observations demonstrate conclusively that it is not legitimate to compare a spastic muscle of a mammal to the "fixing" muscle of a mollusc, on the grounds of parallel metabolic activity. Dusser de Barenne's observation also suggests that a tonic muscle uses energy in the same way as a muscle responding to tetanic stimulation. The early literature concerning this problem will be found in Chapter XVIII of Bayliss (*59*). It may be added that Lovatt Evans (*289*, *290*), in keeping with Dusser de Barenne and Burger, found the O_2 consumption greater in a decerebrate animal before curarization than after.

Bayliss (*59*) observed the same fact, but all authors are agreed that tonic activity involves far less O_2 consumption than tetanic contraction. This is scarcely surprising, for whatever one's working hypothesis be concerning the nature of muscle tonus, phasic responses involve development of tension and doing work, while tonic contraction merely involves the maintenance of tension.

Many investigations have been made purporting to show some relation between *creatin metabolism* and tonic activity. These investigations have

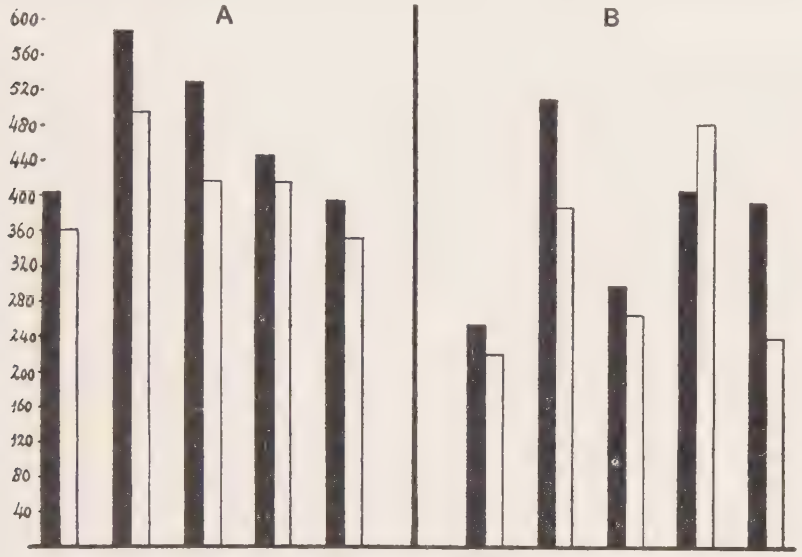

FIG. 163. Diagram showing the differences in respiratory exchange during and after abolition of decerebrate rigidity of a cat. A, oxygen consumption; B, CO_2 output. Black columns, during decerebrate rigidity. White columns, after abolition of rigidity. (Dusser de Barenne and Burger, *Journ. Physiol.*, vol. 59, p. 27, 1924.)

been discussed at length by Cobb (*203*) who concludes that as yet "no satisfactory evidence has been produced that creatin metabolism is in any special way associated with tonic muscular contraction." That creatin is undoubtedly produced by contracting muscles is too well substantiated to admit of any question (*985*), for it is excreted in great amounts after severe exercise, but as Langley (*591*) points out, the evidence indicates that creatin metabolism is in reality more dependent upon somatic innervation than upon sympathetic. This conclusion is strongly supported by Tiegs (*985*) who finds that creatin is given off in large quantities by muscles when fatigued through their motor nerves.

THE FUNCTION OF THE SYMPATHETIC NERVE FIBRES OF SKELETAL MUSCLE.

The painstaking work of Agduhr, Boeke, Dusser de Barenne, Garven, Kuntz and Kerper, and Tello have provided unimpeachable evidence of the existence of non-medullated sympathetic fibres terminating beneath the sarcolemma of skeletal muscle fibres. These endings have been termed "accessory," since the muscle fibres in question possess, in addition, somatic motor innervation. It is quite futile to ignore the evidence of these investigators, as some writers have recently done (*1027, 590, 591*), on the grounds of a disbelief in sympathetic innervation of muscle tonus. The sympathetic endings exist, and it is the duty of physiologists to recognize them and to discover their function.

It was most natural to suspect that they might be concerned in the maintenance of tonus, and those who early approached this difficult question deserve the highest praise for their stimulating work. However, the evidence now at hand excludes, in the writer's opinion, the possibility of direct participation of the sympathetic system in the maintenance of tonic postural contraction. What function then are we to assign to these endings?

Certain unpublished experiments performed by the writer may possibly bear on this question. As they were inconclusive, they did not appear at the time worthy of separate publication, but it is permissible to mention them here. If, in a motor nerve to a muscle, sympathetic fibres exist in association with somatic motor fibres, a stimulus just effective for the somatic fibres will be considerably below the threshold necessary to excite the sympathetic fibres. It has, for instance, been found possible on this basis to separate in an uncut nerve (frog) the efferent from afferent fibres, since the latter have a higher threshold for faradic stimuli than the former (Lutz, *670; 349*). In the case of the sympathetic fibres, the threshold difference is even greater. Consequently, if the sympathetic system modifies the nature of the contraction, one might demonstrate it by recording a motor response a first just-adequate stimulus, and follow that by a similar response elicited by a stimulus which is above the threshold of the sympathetics, as evidenced by vasoconstriction in the cutaneous vessels. For this purpose, short tetani were elicited at a low rate, since sympathetically innervated tissues are often irresponsive to single stimuli or to tetani in which the rate of stimulation is high (*554, 595, 600, 194*). In the case of the frog's gastrocnemius, the femoral artery was placed across the electrodes with the nerve to offset the possibility that sympathetic fibres might run with that vessel (but cf. *592*). With short tetani at 20 to 25 per second it was found that the

response of the frog's gastrocnemius was practically unaltered in its electrical or mechanical aspects when the intensity of stimulation was effective for the sympathetic fibres. However, the tension developed was often considerably greater with stimuli of greatly increased intensity than with *maximal* (for the somatic fibres) stimuli of lower intensity, especially in fatigued muscle. I can offer no explanation for this observation,[5] unless it be due to effects similar to those obtained by Orbeli and his collaborators, whose work we must now consider.

The investigations of Orbeli. Theories of the function of the sympathetic system have been rendered dubious in the past by the absence of adequate positive evidence derived from nerve stimulation. Various observers anticipated that activity of the sympathetic would produce changes in tonus, and the experiments designed to test this failed to disclose what is apparently the true effect of sympathetic stimulation. For the latter discovery, we are indebted to L. A. Orbeli of Petrograd (Leningrad).

Orbeli's student, A. G. Ginetzinsky (*395*), has performed the following important experiment. A gastrocnemius muscle of a frog isolated from the body with complete nerve supply, was stimulated through its VIIIth and IXth anterior lumbar roots by short tetani 5 seconds in duration at intervals of 55 seconds, and isometric records obtained. Under these circumstances the plateau tension developed in each successive response diminishes progressively. However, if during the 55-second intervals the sympathetic roots from the VIIth lumbar ganglion were stimulated, this diminution did not occur during the first five or six tetanic responses. In the first few responses, sympathetic stimulation led to augmentation of the tension developed, but alone it produced no tension. This gives convincing evidence that stimulation of the sympathetic retards the onset of fatigue. Similar experiments have been recorded recently by Orbeli in the Pavlov Jubilee Volume (*742*). Orbeli delivered to an excised muscle repetitive twitches at short intervals, and, when fatigue had commenced to show itself by a diminution in height of successive twitches, the sympathetic was stimulated and after a considerable latency the twitches became augmented, the height of the effect occurring some time after sympathetic stimulation had ceased. Orbeli's graphic record illustrating this is reproduced in figure 164. That the result is not due to escape of stimulating current, is evident from the latency and the prolonged after-continuance of the effect. Secondary circulatory alterations can also be excluded, since isolated muscles were

[5] Further details of these experiments will be published at a later date. The possibility of "supra-maximal," *i.e.*, repetitive, responses to each induction stimulus was excluded by the electrical record.

utilized. It would seem indisputable, therefore, that sympathetic stimulation does influence the activity of skeletal muscle.

Orbeli believes that the sympathetic acts on skeletal muscle as it does in the heart, *i.e.*, it increases the force and amplitude of contraction and enhances the rapidity of development of tension. In conjunction with Lebedinsky, he has found that sympathetic stimulation increases the rate of conduction of the electrical response in a fatigued muscle. Though Orbeli uses the word "tone" in describing his results, its implication is not that of postural tonus, but is used rather in the old sense of "toning up" of a given tissue. In his recent contribution in the Pavlov Jubilee Volume,

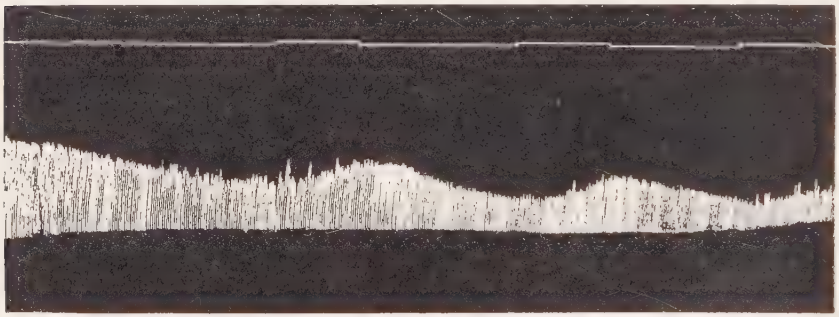

FIG. 164. The effect of stimulation of sympathetic nerves supplying the skeletal muscle of a frog. A series of rapidly recurring twitches were delivered to the motor roots until signs of fatigue appeared, when the lumbar sympathetic nerves were stimulated at intervals indicated by the time signal. After a considerable latency it will be seen that the size of the twitches becomes gradually increased, the maximum effect occurring sometimes after cessation of the sympathetic stimulation. (From L. A. Orbeli, *Pavlov Jubilee Volume*, p. 409, 1924.)

there are certain suggestions as to the possible relation of his experiments to postural tonus, but no definite conclusion is reached. Numerous other experiments confirming previous observations are also reported.

The similarity between the effect of adrenaline on fatigued muscle (excised) and that of sympathetic stimulation, is a most striking and suggestive feature of Orbeli's experiments. It will be recalled that Cannon and Nice (*186*), and Gruber have demonstrated that adrenaline diminishes "fatigue," and it has this effect even when applied to an isolated muscle. Grüber (*417*) has therefore suggested that adrenaline may exert some direct "trophic" action upon the muscle, presumably through a power to facilitate removal of metabolites. Similar conclusions were reached by Lange (*577*, see above, Chapter V). Moreover, M. Lapicque and Nattan-Larrier (*618*)

have demonstrated that adrenaline reduces the chronaxie of a fatigued muscle, an observation which is also in keeping with the assumption that this substance facilitates the removal of acid metabolites. It may be noted in this connection that Beattie and Milroy (*61*) have found that adrenaline influences the synthetic processes of the lactic-acid-hexosephosphate mechanism. The precise nature of this influence, however, is as yet obscure, and it is somewhat doubtful whether it can be adequately worked out by means of analyses of minced muscle (see above, Chapter V).

One may add that the more important metabolic activities, if we may believe Embden's evidence, occur in the sarcoplasm of muscle. Consequently, should it turn out that the sympathetic nervous system does actually influence these metabolic reactions, the belief of the Dutch investigators that the sympathetic nervous system controls the sarcoplasm is, in a rather indirect way, justified. But this of course does not imply that the sympathetic system or the sarcoplasm has anything directly to do with the maintenance of muscle tonus. As we shall presently see, probably the most tenable attitude to take in the present state of knowledge, is that all tonic reactions of skeletal muscle are produced through the integrative action of the nervous system in effecting an appropriate temporal sequence of "all-or-none" responses of individual muscle fibre units.

Orbeli's work has been criticized by Miss Wastl (*1029*), who was unable to confirm Ginetzinsky's experiment on the frog. However, as she utilized an isotonic lever weighted by 15 to 20 grams, which is ill-designed to bring out small differences in force of contraction, it is probably unjustifiable to attach great significance to this negative result,—for carefully controlled positive results are of more weight than a negative result. Moreover, the following passage occurs in the description of her experiments, which suggests that the effect was actually present. "If the strength of the current applied to the sympathetic was slowly increased, a point could be found in a few cases when, probably in consequence of spread of current, the muscle suddenly began to produce higher contractions in the rhythm of the root-stimulation. At this point apparently an escaped current was added to the rhythmic stimulations of the roots and strengthened their effects, *though it was still too weak to excite the roots of itself*." Her failure to observe effects in mammalian muscle is possibly to be attributed to the circulatory effects of sympathetic stimulation.

Orbeli sums up his contentions in the following words (*741*):

"The direct influence of the sympathetic nerves on the skeletal muscle is fixed beyond doubt, the universal significance of the sympathetic innervation is proved, the relation of the autonomous nervous system of the generalized muscular formation is shown and the ability of the autonomous fibres to alter the condition of the muscle and its contents become transferred from a small organ, the heart, to the whole skeletal muscle, thus fulfilling the prophecy of the 'chemical tonus' of E. Pflüger and of the 'trophic innervation' of Pavlov. The sympathetic system which guides all the vital properties of the muscles and secures for them the greatest use of their reserve strength must also affect their tone and metabolism." (Gantt, *377*.)

If we accept Orbeli's conclusions, as set forth in the previous quotation, it is evident that the existence of "trophic" nerves to skeletal muscle may be regarded as established. However, the term "trophic," as applied to nerve fibres, has long aroused uncertainty in the minds of many, partly because of inadequate experimental evidence and partly because the meaning of the word itself is vague. Consequently, it seems more desirable simply to recognize that the sympathetic system *does* influence the activity of skeletal muscles, and then to define as accurately as possible the nature of that influence, rather than to refer to it by an uncertain and undescriptive term. What inferences, then can we draw from Ginetzinsky's and Orbeli's evidence?

Stimulation of sympathetic nerve fibres of a fatigued muscle leads, after a considerable latency, to an increase in the size of successive twitch contractions. This effect has been interpreted as due to a diminution in "fatigue." Now we have reason to believe that fatigue, in the case of muscle, is probably an expression of an accumulation within the fibres of acid metabolites. Indeed, the hydrogen ion, *per se*, appears to be the chief factor in the production of fatigue (*624*, *417*). Are we therefore to suppose that stimulation of the sympathetic facilitates the removal of acid? Since, in Orbeli's experiments, the circulation was cut off, we cannot attribute the results to altered oxygen supply. Consequently, the effect would appear to be due either to liberation of buffer substances, or to an alteration of the hexosphosphate-lactic-acid equilibrium, such that resynthesis of lactic-acid into glycogen occurs. Observations of the pH of muscle before and after sympathetic stimulation have not yet been made, so our initial premise, namely, that sympathetic stimulation facilitates the removal of acid, is as yet unproved. If we grant it as probable, we have as yet no way of deciding in which of the two ways the acid is removed. It is likely, however,—since lactic acid is probably converted into lactate before resynthesis,—that the sympathetic produces its effect through making more available the buffer substances within the muscle.

It is as yet premature to discuss the significance of Orbeli's work in relation to the general physiology of the organism. However, it is evident that if the sympathetic nerve fibres are as universally distributed to skeletal muscle as Boeke, Agduhr, and Kuntz and Kerper would have us suppose, they clearly represent a mechanism of fundamental importance. There would seem little doubt but that this influence is one which increases the "efficiency" (to use the word in a very general sense) of the muscle mechanism; *i.e.*, one which prevents premature fatigue and facilitaties prompt recovery. One need only mention the greatly increased fatiguability of

sympathectomized limbs (*e.g.*, the bird's wing) to which Hunter, Kuntz and Kerper, and others have drawn attention. Undoubtedly, when sufficient experimental evidence is available to enable adequate definition of the function of muscle sympathetics, it will be found to harmonize with the generalized effect of the sympathetic stimulation (*e.g.*, diminution of fatigue) so completely elucidated by Cannon (*185*), Gruber (*412*, *420*) and others. We need to know more concerning the influence of the sympathetic system upon "oxygen debt" following exercise, and indeed more about its effect upon the lactic-acid mechanism itself, before our knowledge will be in any way complete. At present we can only say this, that whatever the function of the sympathetic system may be, it exerts its influence upon the quantal (all-or-none) responses of the individual muscle fibres, and we are, moreover, amply justified in dismissing as unproved and highly improbable the hypothesis that the sympathetic system is directly concerned in the maintenance of reflex postural tonus.

EVIDENCE FOR SOMATIC CONTROL OVER MUSCLE TONUS

Previous observations on the electrical responses in tonic contractions. When rapid oscillations occur in the electromyogram, it is generally agreed that they are due to a rapid succession of action currents in the muscle. The usual explanation suggested for the irregularities in the electromyogram of voluntary contractions is the asynchronous nature of the responses of the individually contracting elements (*774*, *12*, *319*, *365*). We shall consider later the nature of the voluntary electromyogram and devote our attention for the moment to the variations which have been observed in tonic contractions. The question arises as to whether there exists in muscle, mechanisms of contraction which either produce no electrical responses or give rise to potential differences having a very slow time course. For several years this question has been the cause of lively controversy on the Continent, especially in Germany.

Apparent absence of electrical variation in sustained contractions. Foix and Thevénard (*314*) and others (*384*, *631*, *403*; *1041*) have observed that when galvanometer leads are taken from tonically contracting muscles and the tonus for any reason suffers diminution there occurs in the string a continuous movement in the positive direction (down); when the tonus becomes augmented a progressive negative deflection is observed, and this has been urged as an expression of the activity of a so-called "fixing" mechanism which these authors believe to be responsible for muscle spasticity. They compare it with smooth muscle. Similarly Lewy (*631*) and Golla (*401*) have recently brought forward evidence that a constant

deflection of the string is produced when a muscle contracts tonically. This constant movement occurs quite apart from any discontinuous activity which may occur at the same time. Like Foix and Thevénard, Lewy has interpreted this as providing evidence for the dual nature of the muscular mechanism. Evidence of a somewhat different character, but supporting the same general view, was put forward by Wertheim-Salomonson (*1041*). In examining human cases of spastic paraplegia he observed that whereas the knee-jerks and ankle jerks, and also the corresponding clonic responses of the muscles involved in the movement of these joints, give rise to well-defined action currents, the same muscles, when in a high degree of spastic contraction produce no action currents even with the most sensitive recording instruments. Salomonson concluded from this that clonic and jerk contractions of these muscles are produced by the all-or-none mechanism, while the spastic condition results from the activity of the fixing mechanism. In harmony with those observations, Kahn (*535*) found that in the breeding season the forearm muscles of the male frog when maintained in the clasping position are apparently quite free from action currents.

These deductions are, as we shall see, open to certain objections. There is, however, one striking case in which a prolonged contraction, apparently innervated centrally, shows no electric responses even when examined with the most sensitive recording methods. Liljestrand and Magnus (*642*) found that in the "reflex" contraction brought about by injection of tetanus toxin into a muscle or nerve trunk (cats), and in the contracted muscles of human patients suffering from tetanus poisoning, there are absolutely no recordable action currents. This evidence is important, yet in considering it attention may be directed to Sherrington's observations (unpublished) on the action of tetanus toxin. He found that after the toxin has acted for several weeks, cutting of the motor nerves to the muscle leaves the muscle quite as rigid as it was before. In other words, after a time the tetanus toxin produces a state of *direct contracture*. Liljestrand and Magnus's experiments were carefully controlled and in the beginning the tetanus effect had certainly every appearance of being nervous in origin, but in view of the gradually developing direct effect it is extremely difficult to decide where the nervous effect ceases, and where the direct effect of the toxin commences. Even granted that in the early stages the effects are purely nervous in origin, the possibility that the apparent lack of electrical variations was due to the asynchronous nature of the individual fibre responses was not ruled out.

Electrical variations in sustained contraction. Cobb (*200, 201, 202*) and others (*12, 365*) have emphasized that the constant deflections pro-

duced in the galvanometer string during alterations of tonic activity are due, not necessarily to physiological alterations in the muscle, but rather to the shifting of electrode contact on the skin or surface of the muscle and fascia. As shown in figure 165, Einthoven (*269*) observed corresponding deflection in completely denervated muscles when movements corresponding to those involved in contraction were passively imposed upon the muscle itself. He suggested that these might be due to alterations in the demarcation current. However, with the Rehn (*804*) technique of silver chloride electrode such alterations with passive tension variations have usually not been observed (*365*). These constant deflections are attributable therefore, to movement of the leads (especially the zinc sulphate variety). No doubt Foix, Lewy and others have taken the possibility of these sources of error into

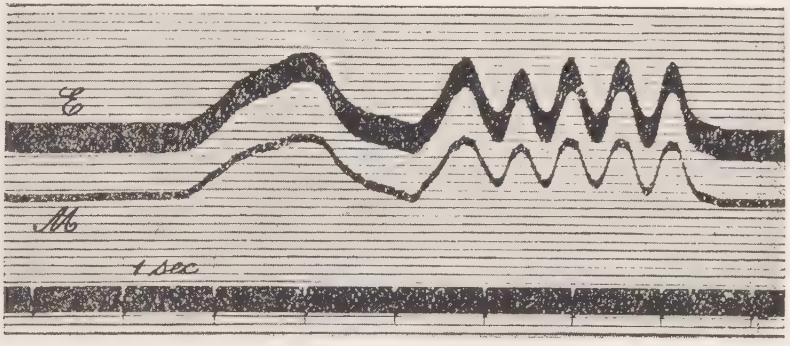

FIG. 165. Einthoven's figure showing the movement of the galvanometer string as a denervated muscle is passively extended and released. (*Arch. Néerland.*, tom. 2, p. 495, 1918.)

account, but in view of Cobb's and Einthoven's observations, the deductions from their findings cannot be accepted without added confirmation. Moreover, in the records taken in the course of the present studies, in which electrical responses were taken under a great variety of conditions, no constant movement of the string was ever observed in the course of a contraction (*e.g.*, fig. 78, Chapter VII), unless skin or fascia touched one of the leading-off electrodes during the contraction. The alterations in demarcation current with differing passive tensions, which de Meyer (*708*), and Einthoven (*269*) have described are, as already mentioned, very slight in extent with silver chloride leads and in many experiments were not demonstrable.

In view of the close similarity between the condition of spastic paraplegia in human patients and decerebrate rigidity in animals, the observations of

Salomonson concerning absence of electrical variations in the former condition would appear to be effectually offset by the discovery of Dusser de Barenne (*252*) and Buytendijk (*183*) that well-marked electrical variations of rapid oscillatory character occur during decerebrate rigidity. Moreover, Dusser de Barenne and Einthoven have shown that these rapid oscillations are inhibitable by the ordinary way in which tonic responses are inhibitable (fig. 168). Hoffmann (*490*) similarly observed that the eye muscles in the normal tonic condition give rise to rapidly rhythmic action currents. This again strongly supports the view that the tension of a tonic muscle is maintained by somatic impulses.

Recent observations on the sexual clasping reflex of the male frog during breeding season also bear out this conclusion. Kahn, as we have seen, failed to find action currents in the resting condition of the frog, but if the animal be interfered with the reflex contraction of these forearm muscles increases and small action currents are momentarily observed, but disappear again when the frog becomes quiet. Spiegel and Sternschein (*963*) observed that this reflex was not affected by the injection of atropin or adrenalin or by sympathectomy, suggesting that the innervation of the reflex is purely somatic. Lullies (*668*) made the interesting observation that the force exerted during the clasp is actually very small so long as the frog remains absolutely quiet, but with the slightest activity the force of the reflex is greatly increased and is accompanied by electrical oscillations. Moreover both Wacholder (*1006*) and Lullies (*668*) find that even in the resting condition very minute oscillations are to be observed in the electromyogram. Consequently, this sustained reflex offers no real objection to the view that sustained contractions are tetanic in character. Lullie's observations that in the resting condition the force exerted is small is in keeping with the similar phenomenon often noted in spastic human patients; such individuals, when at rest, have relatively flaccid muscles, but on attempted movement as during examination by a physician, the muscles become rigid, or—in the literal meaning of the term—"spastic." Moreover, in these spastic conditions of human patients (contrary to Wertheim-Salomonson), Hansen, Hoffmann and Weiszäcker (*435*) have observed minute rhythmic oscillations in the tonically contracting muscle. Stanley Cobb (*201*) obtained an interesting record from the spastic muscles of a patient with *paralysis agitans* in which during the record the tremor observed in the string gradually disappeared and was supplanted by minute irregular oscillations; at this moment, the muscle from which the leads were taken, was observed to pass into a condition of rigidity. This record is reproduced herewith in figure 166. The foregoing observations have recently been discussed

FIG. 166. Case of paralysis agitans. The first five periods of $\frac{1}{5}$ second each (marked by the vertical lines) show the typical action currents of Parkinsonian tremor. The tremor then ceases and there remains only the fine frequent action currents which are probably due to the rigidity. (Cobb, *Arch. Neurol. & Psychiat.*, vol. 8, p. 247, 1922.)

at length by Adrian (*12*) in his Oliver-Sharpey Lectures on the Electromyogram, which the reader may consult for further details. Adrian reaches substantially the same conclusions, namely, that a study of the electromyogram provides no support for the "dual" theory of muscular activity.

Study of the electrical variation, therefore, of tonically contracted muscle yields ample evidence of rhythmic oscillations, which suggests somatic innervation with asynchronous volleys of impulses. Direct proof that such is the case has been provided by an analysis of the stretch reflex.

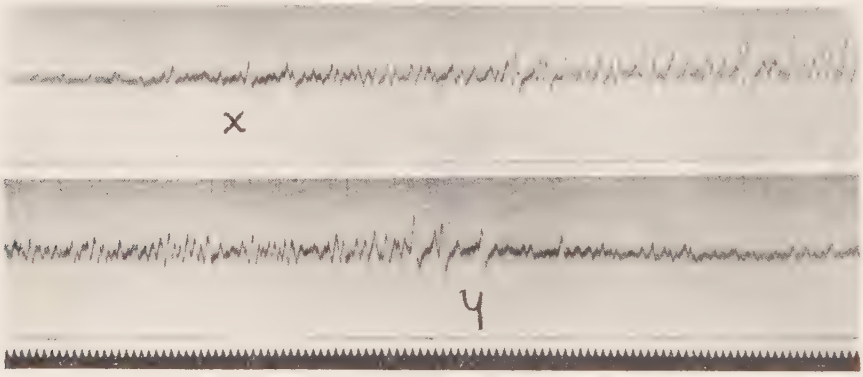

FIG. 167. Amplified electromyograms showing effect of stretching gastrocnemius muscle during decerebrate rigidity. In A, stretching begins at *x* and gradually increases. B begins with applied tension still increasing to maximum (2 200 grams); tension ceases at *y*. Hindle galvanometer; 25,000-ohm, gilded quartz string, 1.5μ diameter, tension 51 m. per ampere. Electron-tube amplification with 0.1 microfarad condenser damping. Magnification 490. (Forbes and Cattell, *Amer. Journ. Physiol.*, vol. 70, p. 161, 1924.)

TONUS AND THE STRETCH REFLEX

It is generally agreed that the condition of decerebrate rigidity is one in which the muscles are in a state of heightened "tonus," or spasticity. It is therefore permissible to examine such a muscle with the aim of studying the features of tonic contraction.

When the patellar tendon of a preparation possessing a high degree of rigidity is detached, and the tension in this way relaxed, the muscle ceases to be rigid. The adequate condition for the maintenance of the rigidity is the slight stretch occasioned by the normal anatomical relations of the muscle. If instead of detaching the tendon an ipsilateral nerve is stimulated the muscle relaxes and becomes, as Sherrington (*886*) has pointed out, indistinguishable from a muscle in which the nerve is cut. It is therefore

evident that a certain degree of elongation of an uninhibited muscle of a decerebrate preparation is necessary for the existence of tonic contraction. With this in mind, we may proceed to examine the electrical responses of muscle in decerebrate rigidity and in the stretch reflex.

Electrical responses in the stretch reflex. Buytendijk (*183*) and Forbes

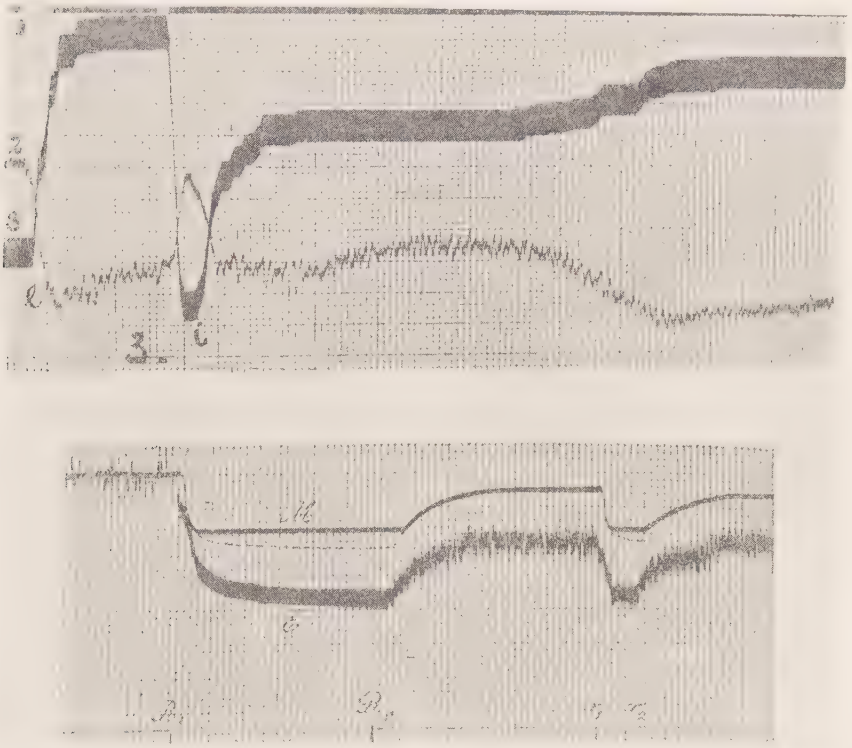

Fig. 168. A. Dusser de Barenne's demonstration of the inhibition of electrical oscillations of a muscle in a decerebrate rigidity (ipsilateral stimulation). (*Central. f. Physiol.*, Bd. 25, p. 335, 1911.)

B. Einthoven's record demonstrating the same fact. (*Arch. Néerland.*, tom. 2, p. 490, 1918.)

and Cattell (*319*), observed that the rhythmic electrical variations of a muscle in decerebrate rigidity tend to become of somewhat greater amplitude when the muscle is placed under stretch (fig. 167). Fulton and Liddell (*365*) noted when silver chloride leads were inserted into the detached patellar tendon and belly of rectus muscle of a decerebrate cat, that *no* elec-

trical responses are to be seen if the muscle is flaccid (*i.e.*, under no tension). When, however, such a muscle was extended by a tension of several hundred grams small rhythmic oscillations were usually observable in the galvanometer record. If an inhibitory nerve were stimulated under these conditions the string of galvanometer again became quiet, as Dusser de Barenne (*252*) and Einthoven (*269*) have previously observed, and the muscle at the same time usually underwent slight relaxation (fig. 168). This relaxation is to be regarded as an inhibition of tonus in accordance with the conception so well established by Sherrington (*886, 922, 925*).

In some preparations, however, a strong inhibitory stimulus causes in addition to the relaxation a small ipsilateral contraction (*364*) which has been considered in a previous chapter. This contraction is probably due to a small proportion of flexor muscle fibres mixed with the quadriceps group. It gives rise mechanically to a small residual contraction showing the rhythm of stimulus which is also shown in the galvanometer string. Following this, however, there is a period of complete inhibition marked by complete quiescence of the string (the post-inhibitory notch, *364*).

Liddell and Sherrington have provided reasons for believing that the knee-jerk of rectus femoris or of quadriceps and also the clonic responses of this muscle are fractional manifestations of the stretch reflex. As is well known, they are both accompanied by well marked action currents (Jolly, *523* Snyder, *952*). In the case of the clonic responses, which may be elicited by attaching the muscle to a weighted isotonic lever, the action currents for each individual contraction of the clonus are sometimes dicrotic and often repetitive in nature, as has been observed by Cobb (*198*) and others (*365*). A question therefore arises as to why when this muscle shows well-defined action currents in its knee-jerk and in clonus, the electrical variations in the stretch reflex may be vanishingly small. When the muscle is gradually and uniformly stretched, thus evoking its stretch reflex, the galvanometer string may be almost entirely at rest showing only the slightest Dusser de Barenne-Buytendijk vibration at the height of a reflex response of several kilos. If the reflex is inhibited, this small vibration, as we have seen, disappears.

When, however, the stretch reflex is elicited without absolute uniformity of stretch,—when, in other words, the table delivering the stretch falls irregularly,—relatively large action currents are to be observed *immediately after each irregularity in the descent of the table*. The size of the action current caused in this way varies with the extent of the irregularity in the stretch. That this movement of the string is physiological, and not a fortuitous deflection caused by shifting of contact, is evident since the deflection always follows at an interval of 6 to 9σ after the irregularity (see fig. 169), and a

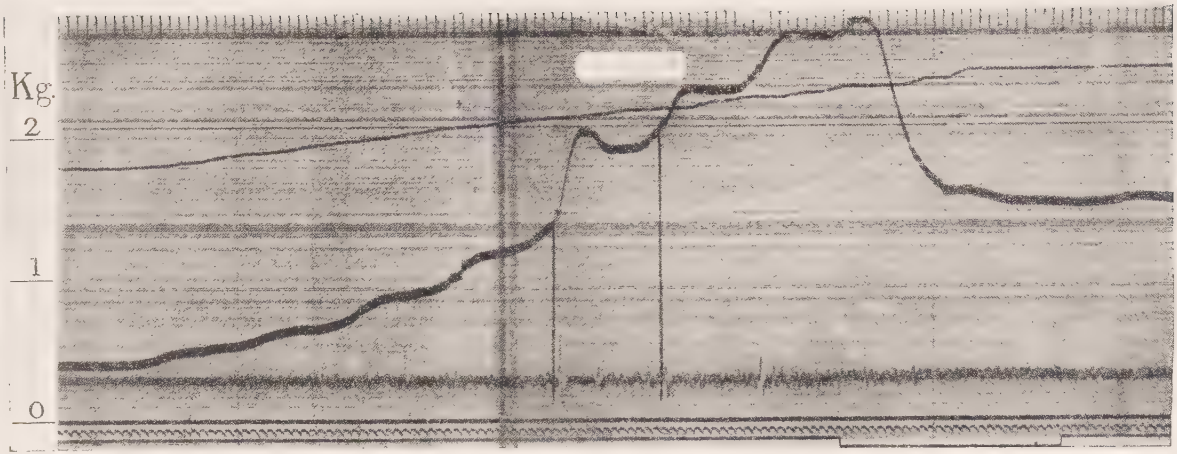

FIG. 169. Quadriceps femoris of decerebrate cat, showing a myotatic reflex in response to a slow stretch. Muscle initially at 600 grams tension. A stretch of 3 mm. was given in 1.5 seconds, during which the tendon was tapped. The taps are indicated by abrupt upstrokes in the myographic record. The tap in approximately the middle of the ascent is the most effective, as it is followed after 7σ by an action current and characteristic (knee-jerk) contraction, which fuses with the increasing active tension. The perpendicular dropped from the tap on the myograph to the string shows the 7σ interval. At the height of the stretch the muscle is inhibited by a weak tetanic stimulus applied to the ipsilateral sciatic nerve for an interval indicated by the lower signal. Rate of inhibitory stimulation (50 per second) indicated by vibrating signal immediately above. Line of zero tension above vibrator. Galvanometer string between myograph and line of zero tension. Leads two silver pins 0.6 mm. diameter coated with chloride. Fall of the stretching table shown by sloping line near top of the plate. Time above = 0.02 second. Tendon movement magnified 80 × in all figures. (*365*.)

well-defined hump on the mechanical record follows in turn after this movement of the string. Without an accurate mechanical record, it is clear that it is impossible to interpret these electrical responses.

The irregularities in the fall of the table may be readily imitated by tapping of the tendon during the phasic period of the stretch. These taps give rise to sudden increases in tension and mechanically the reflex responses to such taps are in every way comparable to knee-jerks. They fuse, moreover, with the increasing active tension produced by the uniformly increasing stretch. Such taps give rise to action currents which also fall at an interval of 6 to 9σ after the tap. These action currents in the majority of the records examined are much larger than those produced by irregularity in the fall of the table.

It has been pointed out (Chapter XI) that in the case of even the simplest myotatic reflex, the knee-jerk, that responses of the individual muscle elements are never quite in phase. With a stretch reflex elicited by an evenly progressive stretch, it is clear that there will be a gradual "recruitment" of the afferent endings, and the more uniform the stretch the more complete will be the resulting asynchronism of the afferent stimuli. The responses of the end-organs, in other words, occur *serially*. "The galvanometer string under these circumstances may be likened to a Brownian particle under bombardment almost indiscriminately in all directions. Like the Brownian particle, the string only occasionally has a sufficiently large number of action currents impinging upon it simultaneously to produce deflection. However, when the table falls in irregular steps, or when a tap is given, relatively large numbers of afferent endings in the muscle would be stimulated simultaneously with the result that the corresponding proportion of efferent motoneurones would be stimulated in unison" (*365*). In other words, the absence of electrical responses in sustained stretch reflexes is precisely what one would anticipate on *a priori* grounds.

This interpretation is amply supported by Adrian and Zotterman's (*19*, p. 156) analysis of the response to stretch of the end-organs in the m. sterno-cutaneus (frog) in which when more than one end-organ responded during a continuous stretch the responses were invariably out of phase with each other.

Leads taken to the galvanometer directly from the anterior crural nerve have given the same result, though owing to the smaller size of the electrical variation it was less capable of accurate interpretation (*365*).

Discussion. We have seen that the minute and variable character of the electrical responses of muscles in decerebrate rigidity and other tonic manifestations has led many writers to the inference that postural reactions, especially when exaggerated, are facilitated by some "contractural" or

fixing mechanism other than the all-or-none type of response known to occur in individual muscle fibres when their motor nerve is stimulated, Now the postural response which gives rise to decerebrate rigidity *is* the stretch reflex. *In the elicitation of the stretch reflex, therefore, we have* "tonus in its making." The adequate stimulus for the development of tonic rigidity in the decerebrate animal is the slight stretch occasioned by the normal anatomical attachments of the muscle, and it has been pointed out that when an extensor muscle of a decerebrate preparation is detached from its tendon and allowed to hang loose (or if completely inhibited), there is no trace of any electrical response. In other words there is no active contraction under such circumstances and consequently no rigidity. Yet clearly defined electrical responses occur when the stimulus (stretch) for the development of the postural reaction occurs with sufficient abruptness to stimulate a large number of afferent endings approximately simultaneously. Postural reactions of this type may therefore be accounted for in terms of one sort of contractile response, *viz.*, the all-or-none contraction of individual muscle fibres which have been so thoroughly studied in peripheral nerve-muscle preparations. "It would appear from this that one of the great integrative functions of the central nervous system,—which makes possible steady sustained responses,—is the production of completely asynchronous responses of individual muscle elements."

The relative unfatiguability of postural reactions has been urged by many writers as being incompatible with the all-or-none view concerning the origin of posture. Barbour and Stiles (*53*, p. 75) and Forbes (*318*, p. 403), however, have suggested that muscle elements in all probability respond in rotation. Thus Barbour and Stiles suggested in 1912 that an asynchronous "form of nervous discharge must give rise to alternate movements in neighboring elements of the muscle, one set of fibres shortening while others relax. The resulting tension may however be fairly uniform." In favour of this it has been noted (*365*) in the motor-responses of extensor muscles (cats, weighing 2 kilos) that tension as great as 40 to 50 kilos may sometimes be developed, but in postural responses or in any other type of reflex response the tension developed is seldom greater than 5 to 6 kilos. In view of the well-known relatively quick fatiguability of the motor nerve tetanus and the fact that postural responses, though they decline somewhat at first, eventually reach a steady height which may last for 30 minutes or more, it is unbelievable that in the postural responses the same fibres are in activity the entire time.

Proof that pale fibres participate tetanically in postural responses. Perhaps the most convincing evidence favouring the view that the stretch

reflex is made up of all-or-none responses of individual muscle units has come from a study of the inhibition of the stretch reflex. In the early chapters of the present monograph we have studied the features of the responses of individual muscle elements especially with reference to the duration of the response. We know that a given neuromuscular twitch requires 35 to 40σ to complete itself, and that this duration may be somewhat less when the individual muscle elements have shortened. We know also that the sluggish adductor muscles of *pecten*, to whose activity the plastic features of mammalian muscle have often been compared, relax much more sluggishly than the striated muscles in this mollusc. It is a fair inference consequently that if the stretch reflex (which as we shall see in the next chapter is largely responsible for the property of "plasticity") owes its existence to such a sluggish form of contraction as that exhibited by the fixing muscles of molluscs, it would require some little time to inhibit it. Careful analysis of the rate of inhibition from the stretch reflex has shown that strong inhibitory stimulation causes an inhibition which is as rapid as that following the cessation of a motor tetanus (*365*). Liddell and Sherrington observed the same phenomenon in the case of inhibition of the crossed extensor reflex (*641*). The commencement of the relaxation is not, however, characterized by a sharp "angle," the reasons for this having already been elucidated in the chapter (XIII) on inhibition. The rate of inhibition, in other words, appears to provide direct evidence that the fibre mechanism participating in the stretch reflex is none other than that which responds when the motor nerve is stimulated. The participating fibres cannot, for instance, be red, for unpublished experiments (*205*) have shown that the rate of relaxation of red muscle (soleus) of the cat is as much as four to five times slower than that of white muscle (isometric records of motor nerve stimulation).

"Since increase in tension appears to be the adequate stimulus for the proprioceptive endings of postural (myotatic) responses, shifting of the incidence of tension among the afferent endings suggests itself as a cause of the rotation in the response of the muscle elements. It will be recalled that myotatic reflexes are local in their effect (Chapter XV), the reflex, being confined to the particular portion of muscle stimulated (*i.e.*, stretched). Presumably the smallest locus or reflex unit is the group of motor fibres controlled by one 'stretch-afferent' organ. At any given moment in a rigid muscle only a small number of these afferent-efferent systems are active. One would suppose that when such an afferent ending is stretched, the motor fibres controlled by it would contract and relieve the stretch on their own afferent ending, thereby removing their own

stimulus. If other stretch-afferents are stimulated as a result of this cessation of support in the first afferent-efferent system, or if the first system suffers depression, as by autogenous inhibition arising from other types of afferent-ending (*e.g.*, "pain" endings) in the muscle, then neighbouring afferent-efferent systems would become active and thus maintain the state of rigidity in the muscle. So the process might be conceived of as progressing indefinitely in endless asynchronous rotation (*365*)."

This in very general terms is the view of tonic activity which holds that all the phenomena of muscular activity are explicable on the basis of one general type of reaction. It has the advantage (1) of not calling upon an hypothetical muscular mechanism whose existence has never been demonstrated by direct experiment; (2) of providing a workable conception of the nature of the coöperation between phasic and tonic activities of muscle. "Every movement starts and ends in some posture" (Magnus, *680*, p. 339), or, as someone else has expressed it, "tonus follows movement like a shadow" (*507*). In addition, as Redfield has emphasized (*798*, p. 914), "Not only must the muscles assume a new tonic state in each new position of the body, but the tone of the muscles must alter rapidly and in harmony with voluntary and reflex contraction of a tetanic nature." How this coalescence between the tonic condition and the state of active contraction is brought about will be considered in the following chapters.

SUMMARY

Though sympathetic nerve fibres may terminate hypolemmaly in certain muscles, there is no clear evidence that the sympathetic nervous system, as such, is directly concerned in the control of muscle tonus. The difficulties in the views put foward by Bottazzi, de Boer, Hunter, Langelaan, and others have been pointed out, and they are regarded as untenable in their present form. Orbeli's work appears to harmonize many of the conflicting observations in this field. He has found that sympathetic stimulation during tetanic responses retards the development of fatigue much as does adrenaline (excised muscle), and that when a muscle is fatigued, activity of the sympathetic accelerates recovery. These observations suggest that the sympathetic nerves influence the "metabolic" activity of muscle fibres, possibly facilitating the removal of acid metabolites.

If the sympathetic system influences the metabolism of muscle, then, since the chief metabolic activities of muscle appear to occur in the sarcoplasm (Embden), there is a somewhat indirect justification for the belief that the sympathetic fibres govern sarcoplasmic activity. The belief that the sarcoplasm itself produces tonus is, however, without experimental founda-

tion. The phenomena observed following sympathectomy,—the most protean of which is increased susceptibility to fatigue,—are attributable, probably entirely, to secondary circulatory and "metabolic" changes.

A more adequate explanation of muscle tonus is that it is a proprioceptive reflex. To simplify analysis, we may exclude as Magnus has done such proprioceptor influence as might originate in the labyrinth and neck regions, by section of appropriate nerves. Under these circumstances, an unstretched muscle of a decerebrate preparation is without tonus. A muscle extended by the normal anatomical attachments of the body framework possesses tonus. Stretch, therefore, appears to be the adequate stimulus for the maintenance of the tonic condition: "in the stretch reflex, we have tonus in its making." To prove that the elements responsible for the maintenance of tension in a tonic muscle are those which contract when a motor nerve is stimulated, it has been shown that the rate of relaxation from a tonic reaction (when inhibited centrally) approximates that observed for the rate of relaxation of a motor nerve tetanus. From this the conclusion has been drawn that the "all-or-none" fibre contractions responsible for a motor tetanus also give rise to the stretch reflex. Owing, however, to the normal temporal dispersion of fibre activity in the stretch reflex, action currents are not ordinarily apparent in this type of activity. When, however, afferent endings are stimulated synchronously by an abrupt stretch of the muscle, action currents invariably appear in the responding muscle after a latency of $\pm 7\sigma$. On the basis of these arguments, the stretch reflex, and tonic reactions in general, are held to be explicable in terms of the all-or-none principle.

CHAPTER XVII

The Lengthening and Shortening Reactions and the Proprioceptive System

Pertinent to a consideration of muscle tonus is an analysis of the so-called "lengthening" and "shortening" reactions, *i.e.*, the "plastic" element of muscular activity. If a "chronic" spinal or a decerebrate preparation be so supported under the abdomen that the hind limbs hang free, it is found that on passively moving one of the hind legs in such a way as to extend the knee joint, the extended posture so induced remains after removal of the observer's hand,—it being maintained by the tonic contraction of the extensor muscle. If now the observer attempts forcibly to flex the knee, the extensor muscle then opposes the forced flexion with considerable resistance. The shortening of the extensor muscle when its two end-points are passively approximated, together with the resistance encountered on subsequently attempting to lengthen it, constitutes the "shortening reaction" (*915*, *919*, *927*).

If, after the "shortening reaction" has been elicited, the observer (by pressing the ankle) bend the knee forcefully against the resistance offered by the extensor muscles, he will feel at first considerable opposition, especially if the movement be carried out rapidly, but this resistance suddenly gives way and the knee can then be flexed with little difficulty. On releasing the ankle, the knee is found to remain flexed at approximately the angle to which it had been carried by the manipulation. The tonic contraction of the "shortening reaction" appears to have vanished under the pressure of the forced extension. This then is the "lengthening reaction" and it, with the converse "shortening reaction," confer upon a muscle in which they are to be elicited, properties which have appropriately been termed "plasticity." We will now proceed to examine these reactions more in detail.

For this purpose the quadriceps femoris of the decerebrate cat[1] has proved the most satisfactory muscle for detailed study. The method of making

[1] The difference between the "lengthening" and "shortening" reactions as observed in decerebrate and (chronic) spinal animals lies in the fact that in the spinal they are less perfectly graded. They are, however, readily elicited in chronic spinal animals especially in the dog (*919*, p. 111).

the preparation is described in the Appendix. It may be mentioned that, as with the stretch reflex, *the operation demands complete immobilization, either by nerve section or tendon resection, of all other muscles in both hind limbs except the quadriceps extensor, which is being examined.* The cutaneous nerves are also severed so that there is no possibility of extraneous reflex influence coming from this source.

Examination of this reaction, as its name implies, necessitates the use of a recording method which permits of ample movement of the tendon (shortening of the muscle as a whole). It cannot therefore be studied satisfactorily with an "isometric" torsion-wire lever, though slight manifestations of the "shortening reaction" are observed in records obtained with

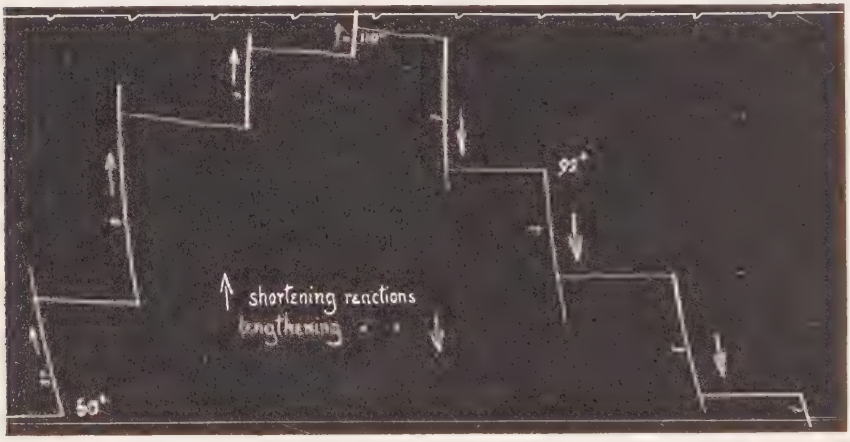

FIG. 170. Isolated vastocrureus: decerebrate cat; *s, s, s, s,* "shortening reactions;" *l, l, l, l,* "lengthening reactions;" 60° and 110° mark the angle of the knee in the respective postures. (Sherrington, *Quart. Journ. Exper. Physiol.*, vol. 2, p. 118, 1909.)

this instrument (see below). For adequate analysis, it is essential to use an isotonic lever or a spring lever which permits of extensive shortening without great alteration of tension. Though these methods are requisite for obtaining graphic records of the reaction, it is nevertheless possible to observe the following features concerning the "shortening reaction" with the naked eye.

THE "SHORTENING REACTION"

The "shortening reaction" occurs: (1) In the fully isolated quadriceps, *i.e.*, it may be obtained after the tendon has been removed from its insertion and after the muscle has been fully debarred from all extrinsic reflex influence such as that which might come from the antagonistic flexor muscles.

This proves that the reaction depends either upon some property inherent in the muscle itself or upon the influence exerted upon it by its own efferent-afferent nerve supply. (2) It is characterized by a delicate gradation of intensity according as the passive movement imposed upon the muscle is great or small in extent, *e.g.*, if allowed to shorten only 1 mm. it will immediately take up its new posture at this new length (fig. 170). (3) The reaction disappears completely on severing the motor nerve. It does not therefore depend upon any property inherent in the muscle itself (Galen). It disappears, moreover when the posterior root supply of the muscle has been severed, and it cannot be elicited when such a deafferented muscle is activated by varying degrees of reflex contraction evoked through excitation of an extrinsic afferent nerve. The "shortening reaction," therefore, does not depend upon contraction *per se*, but is clearly referrable to the integrity of the *intrinsic*[2] afferent nerve supply of the muscle. Further evidence of its reflex nature is supplied by the following important observations.

The "shortening reaction" often shows itself as a terminal phenomenon (T. Graham Brown, *160*) of many reflexes. Thus when a crossed extensor reflex is elicited (electrically or by Philippson's reflex) in a quadriceps in which the degree of freedom for shortening is ample, the "shortening reaction" appends itself to the reflex contraction when the latter commences to subside. This gives to the reflex contraction the appearance of prolonged after-discharge, and it is important to distinguish between the true or "plateau" after-discharge (fig. 171; see below) caused by repetitive "firing" due to the *original* stimulus, and the appended reflex effect due to the "shortening reaction." The distinction between the two is easily made by recording the crossed extensor reflex before and after deafferentation. In the deafferented muscle, though there is often considerable "plateau" after-discharge, the autogenous proprioceptive "shortening reaction" is not present and the muscle in consequence usually relaxes with great rapidity once the tension commences to fall.

Another feature of the "shortening reaction" is that it "seems to graft itself upon the reflex contraction more perfectly than upon a shortening produced passively, and to be itself more perfect when elicited by active contraction than by mere passive extension of the knee under external mechanical manipulation." (Sherrington, *919*, p. 133.) Often there is no feature of a curve which betrays the actual point of union between the pure after-discharge and the appended stretch reflex,—a fact which, as we will see, often renders analysis somewhat difficult.

[2] It is convenient to refer to the afferent nerves supplying a given muscle itself as "intrinsic afferents" while any other afferent nerves exerting a reflex effect upon the muscle are referred to as "extrinsic afferents" (Sherrington, *919*, p. 126).

It would appear from this that the evidence for the "shortening reaction" being a reflex is almost overwhelming. However, as Sherrington (*910*) has pointed out, it is just possible that the reaction is dependent in some way upon the integrity of the nerve supply, as Waller (*1914*) believed of the knee-jerk, without being directly a reflex effect. When the "shortening reaction" was first described the stretch reflex had not been studied, and, as this reaction appears to throw much light on the "shortening reaction," we may profitably consider the relation between the two in some detail.

THE STRETCH REFLEX AND THE "SHORTENING REACTION"

Sherrington (*915*) noted in his first description of the "shortening reaction" that when it was elicited, the leg, on being released from the passive extension of the knee, often drops a little from the full posture thus given to it before becoming "fixed" in its new position. He suggested, "that the drop of the limb released by the manipulator actually excites, by the slight stretch it gives to vastocrureus, a tonic reflex in that muscle, and that the check in the fall of the leg is due to a tonic contraction not previously present but now excited from the muscle by the stretching action of the fall itself." Further consideration of this view led originally to the conclusion that it was somewhat unlikely because (1) the "lengthening reaction," as we have seen, is also evoked by passive stretch of the muscle and (2) because the "shortening reaction" was observed not infrequently to append itself to reflexes and to passive shortening without any dropping back of the knee. In the light of present knowledge these do not seem to be serious objections, especially in view of the complete inadequacy of the alternative "Wallerian" explanation. Let us take the first objection that "lengthening reaction" is also evoked by a passive stretch. This is clearly true, but, as we shall see, passive stretch, when slight, tends to evoke reflex contraction, or at least the predominating effect is always reflex contraction. When, however, the passive stretch is severe and persistent, nociceptive muscle afferents ("pain" endings), among other things, are stimulated, the predominating effect then becomes reflex inhibition, and under such circumstances one observes the "lengthening reaction." Small degrees of passive stretch such as an extension of the muscle tendon by 2 mm. in 0.5 second, invariably leads in the decerebrate quadriceps muscle to a stretch reflex, *i.e.*, to a predominance of reflex contraction, and this is apparently true within physiological limits for all ranges of *initial* length of the muscle.

(2) That the "shortening reaction" is occasionally evoked without a dropping of the limb also does not appear to be a serious objection to what may be called the myotatic conception of the "shortening reaction." The

extremely short latency (*365*) of the stretch reflex (6 to 7σ) makes it evident that the slightest tendency toward a falling of the limb would cause it to be so quickly "caught up" by the resulting reflex contraction that the fall itself would be scarcely perceptible. In fact the extreme speed of reaction of the stretch reflex renders it difficult to understand why a dropping of the leg ever does occur before the reflex is evoked. This however, may possibly be accounted for by the taking up of slack in the patellar tendon before the weight of the limb affects the muscle afferents, and the extent of the slack would certainly vary under different circumstances.

In the present state of knowledge, there is certainly no valid reason for looking upon the "shortening reaction" as other than a manifestation of the stretch reflex. Since the stretch reflex is caused by the all-or-none activity of individual muscle units it follows that the "shortening reaction" must have a similar origin, and is therefore interpretable on the basis of asynchronous multifibre summation (Chapter IV).

THE "LENGTHENING REACTION"

The evidence for the reflex nature of the "lengthening reaction" is similar to that for the "shortening reaction," and may be summarized as follows. (1) It occurs in the fully isolated quadriceps muscle, and (2) is graded in intensity as is the "shortening reaction;" (3) it is not to be elicited in a deafferented muscle, either when the muscle is at rest or when under varying degrees of reflex contraction; (4) it disappears under light anaesthesia as with other reflexes; (5) being in the nature of a relaxation, it is similar to such inhibitory relaxations as are produced by stimulation of the central end of an ipsilateral afferent nerve (*e.g.*, one of the nerves to the quadriceps itself); (6) when the muscle is palpated and the "lengthening reaction" evoked, the feeling is in every way similar to that which occurs in response to reflex inhibition, *e.g.*, of the stretch reflex. There is thus ample evidence of the reflex nature of the "lengthening reaction," and the evidence suggests that it is in fact a reflex inhibition. We may now examine other confirmatory evidence of the inhibitory nature of the "lengthening reaction."

It was noted in the chapter on the stretch reflex that stimulation of the central cut end of one of the four nerves to quadriceps results in reflex inhibition of the remaining three parts of the muscle (Sherrington, *886*). There is no doubt therefore but that the muscle is richly supplied with inhibitory afferent nerve endings. Provided the stimuli are of adequate intensity, the inhibitory effect is seen whatever the *rate* of stimulation may be, and may even be produced by a *single* stimulus. Perhaps the best way

of proving that reflex inhibition does occur in the "shortening reaction" is to find some manifestation of the inhibitory stimulation other than that which one asumes to be produced in the muscle itself. We know, for instance, that a stimulus which inhibits the quadriceps of one hind limb causes reflex contraction of the extensors in the opposite limb. *It follows from this that if the "lengthening reaction" be due to inhibition, the inhibition should manifest itself in the crossed extensor by active contraction, and this is precisely what does occur in Philippson's (772) reflex.* Thus, when the quadriceps of one hind limb is stretched with sufficient intensity to elicit the "lengthening reaction," the opposite quadriceps contracts, and Sherrington (*919*) has stated that in his experience Philippson's reflex is never to be obtained without the "lengthening reaction." Moreover, if the quadriceps is stretched only sufficiently to evoke a stretch reflex, the crossed contraction of the extensor does *not* occur. Coincident with the "lengthening reaction" in an extensor muscle there is contraction of the antagonistic flexors on the same side, which is again in harmony with the observations on Philippson's reflex. It would indeed be difficult to find evidence more satisfactory than this of the inhibitory nature of the reaction. Several additional points, however, may be mentioned.

On first thought the stretch reflex appears to be the direct antithesis of the "lengthening reaction," but a common experience to those who have worked with the stretch reflex is the occurrence of an elongation of the muscle when a stretch reflex is allowed to continue for some time. In fact, the sloping nature of the "static" phase of a stretch reflex may be taken as evidence of the gradual operation of the "lengthening reaction" (figs. 149, 150). Moreover, Sherrington (*919*, p. 150) has observed that manipulations of the muscle such as kneading or poking it in various spots can be seen to produce partial elongation of the muscle. Even, "running the blunt end of a seeker along the lines of attachment of the muscle at the sides of the lower part of the shaft of the femur causes similar smart partial elongations of the muscle. These reactions are obviously reflex inhibitions. They seem referable to mechanical excitation of inhibitory afferents belonging to the muscle and distributed within it." It is therefore highly probable that severe stretch, such as one undoubtedly exerts when assisted by the leverage of the leg on the knee joint, stimulates the inhibitory afferents and in this way evokes relaxation. It seems possible also that the progressive deterioration of the stretch reflex (which frequently occurs all too rapidly) on exposure of the muscle, is attributable to inflammation with the resulting stimulation of these inhibitory afferents,—some of which are most certainly "pain" endings, especially from the edges of the operative wound.

An interesting point concerning the "lengthening reaction" is to determine whether the inhibitory afferents are stimulated continuously after the "lengthening reaction" has occurred, or whether the inhibitory stimulation confines itself merely to the period of forced stretching. Since inhibitory and excitatory stimuli sum algebraically (Chapter XIV), this can very easily be tested by determining the threshold of stimulation during and after the "lengthening reaction" has been evoked. Sherrington (*919*) failed to detect any clear difference in the threshold for reflex excitation of the quadriceps,—either for excitatory or inhibitory stimulation,—when the length of the muscle had been increased by the "lengthening reaction" or decreased by the "shortening reaction." It is evident from this that these respective reactions do not perceptibly alter the excitatory condition of the reflex arc. One cannot therefore regard the "lengthening reaction" as a condition in which the central neurones are subjected to continuous inhibition. It is unlikely then that the duration of the inhibition necessary to produce the "lengthening reaction" is any greater than the period of the forced stretch.

Strychnine in moderate doses destroys the "lengthening reaction." This we may interpret as we have other apparent strychnine inhibitory "reversals" (see Chapter XVIII), as due, not to a conversion of inhibition into excitation but merely to an augmentation of the excitatory reflex. In other words when under strychnine the predominant effect of stretching an antigravity muscle becomes reflex excitation.

To summarize: The "lengthening" and "shortening" reactions are both reflex in nature, the "shortening reaction" being indistinguishable from the stretch reflex, the "lengthening reaction" being a reflex inhibition brought about by the stimulation of inhibitory (probably nociceptive) afferents within the muscle. It is evident from this that the plasticity of muscle is explicable in terms of the reflex coördination and integration of the all-or-none responses of the individual muscle units, the assumption of special "fixing" mechanisms being quite unnecessary to account for this property of skeletal muscle.

THE INFLUENCE OF THE PROPRIOCEPTIVE ARC ON THE CROSSED EXTENSOR REFLEX

Crossed extensor reflexes, as examined myographically, have often been recorded under approximately isometric conditions, *i.e.*, the degree of freedom for shortening has usually not been great (*e.g.*, 0.1 to 1 mm.). Under such circumstances we would not expect the "shortening reaction" to play a large part in modifying the terminal after-discharge of this reflex.

It is reasonable, however, to anticipate some modification even under completely isometric conditions of reflex contraction, for it is impossible in a diagonal fibred muscle (Chapter IV) wholly to prevent shortening of the individual muscle elements. With this in mind, we may consider the differences which have been observed between the "normal" and the deafferented reactions of vastocrureus preparations. By "normal" muscle is meant one with its proprioceptive root supply intact.

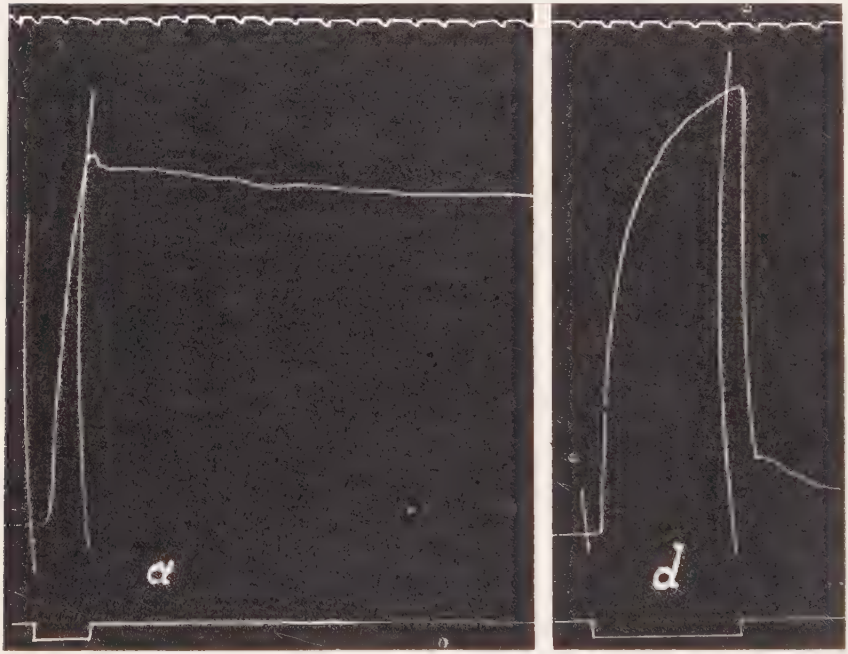

FIG. 171. Crossed extensor reflex of isolated vastocrureus (cat); *a* shows response of muscle with afferent roots intact; *d*, same muscle with afferents cut two hours previously. Note that the "plateau" after discharge is shorter in *a* and *d*, but that in *a* after a slight decline from the true plateau there is appended a prolonged shortening reaction. (Sherrington, *Quart. Journ. Exper. Physiol.*, vol. 2, p. 136, 1909.)

If in the same animal the vastocrureus is deafferented on one side and allowed to remain undeafferented on the other, the following differences, some of which we have already considered, are to be observed. (1) The deafferented muscle shows no decerebrate rigidity even when the decerebration is performed at intervals ranging from two hours to 140 days after deafferenting. This, with the fact that the decerebrate rigidity is

normal in the vastocrureus after severance of every other nerve of both hind limbs except the nerve to vastocrureus, shows that the heightened reflex tonus of decerebrate rigidity depends upon the integrity of the proprioceptive nerves. (2) The normal preparation always exhibits a knee-jerk, the deafferented preparation never does, even when the muscle is under reflex excitation from an extrinsic afferent nerve. (3) The "lengthening" and "shortening" reactions present in the normal muscle are completely absent from the deafferented muscle. In other words, plasticity, in the sense in which it is used in the present monograph, is completely absent from a deafferented muscle. (4) In their after-discharge, normal and deafferented muscles present certain important differences. Sherrington (*919*) observed in his analysis of the "shortening reaction" that the after-discharge was apparently very much less in the deafferented preparation than in the normal, but he attributed this difference in large measure to the tendency of the "shortening reaction" to append itself to the relaxation from crossed extensor stimulation (fig. 171), and he pointed out that in many records it was impossible to say where after-discharge ceased and the "shortening reaction" commenced. He noted that relaxation of a deafferented muscle (crossed reflex) may be so rapid that the leg on falling back to its flexed posture gives a "vibratory shake." His records (*919*) however, show an appreciable amount of "plateau" after-discharge in the deafferented muscle, and in his records of normal muscles in which it is possible to distinguish "plateau after-discharge" from the "shortening reaction," the "plateau after-discharge" is of distinctly greater duration in the deafferented response (see fig. 171).

Recently simultaneous mechanical and electrical records of the crossed extension reflex have been obtained both before and after (*i.e.*, within an hour) section intradurally of appropriate posterior roots (*365*). It was found in such preparations after posterior root section, that the galvanometer string showed in the majority of records no indication of "primary" waves such as were found in the responses before section of the roots (fig. 172). It will be remembered that "primary" waves are those showing the rhythm of excitatory stimulation. The primary waves seemed in fact to be smothered from the start by numerous secondary waves which were, (*a*) Of more rapid onset, (*b*) Of more considerable amplitude than before, and (*c*) Of greater frequency. These results are somewhat out of harmony with those recently reported by Dusser de Barenne and Brevée (*259*), but the experimental conditions in the two instances were quite different, since the latter authors used novocaine for deafferentiation.

Mechanically, the responses of a deafferented muscle in this reflex are

characterized by a more rapid onset, a shorter latency, a sharper ascent-plateau turn, a flatter plateau, and a more rapid relaxation. It approached in general contour the shape of the flexor reflex, but it differed from a flexor reflex in being characterized by prolonged "plateau" after-discharge.

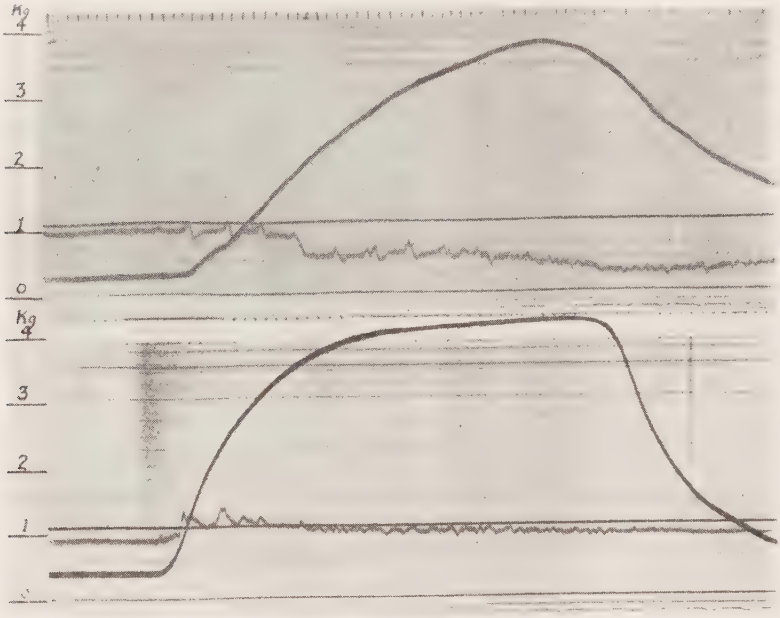

FIG. 172. Crossed extension reflex *before* severing posterior roots. Rate of stimulation, 14 per second; duration of excitation indicated by short-circuiting signal below line of zero tension. Note distinctness of primary waves and the rhythm in the early part of the ascent of the myograph. The slight extraneous movement of the string was due to electrode movement.

FIG. 173. The same reflex of the same preparation two hours *after* cutting, intradurally, the posterior root supply of the muscle. The same strength, duration and rate of stimulation used in both, and the initial tension of the muscle was approximately equal in the two responses. There is a slight initial extraneous movement of string, and a complete or nearly complete absence of primary waves, with a corresponding lack of rhythm in the myograph. Contrast the shape of the mechanical response with that in 172; compare also the respective durations of after-discharge. (*364*)

Other things being equal, the stimulus rhythmn is less apparent after deafferentiation than before, and this is in keeping with the absence of primary waves in the string record. The observations on the secondary waves would appear to indicate that repetitive discharge is less restricted

after posterior root section than before, and that when the motoneurones supplying quadriceps are "released" from their proprioceptive nerve supply, these centres are deprived of an important controlling and integrative influence. It would appear moreover that a factor in proprioceptive coördination of movement is the prevention, presumably by autogenous inhibition, of too rapid onset of response of reflex origin.

After-discharge. Fulton and Liddell observed that the crossed extension reflex of an acutely deafferented muscle showed prolonged "plateau' after-discharge. In the majority of deafferented responses the "plateau" after-discharge was more prolonged than the "plateau" after-discharge of the responses of the same muscle before the posterior roots were cut (see fig. 173). The actual interval, however, between cessation of stimuli and the return of the myograph to the base line was always greater in the

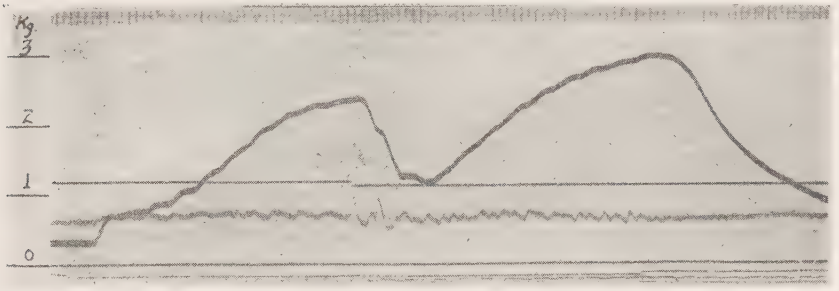

FIG. 174. An inhibition evoked by a moderately strong single break-shock at a point shown by the signal. The result of the inhibition is an enhancement of four primary excitatory waves, with a diminution of secondary waves. Note the two-stepped ascent and the distinct "primary" rhythm. (*364*)

undeafferented muscle, in other words, when the posterior roots are intact the tension attained in the plateau declined less rapidly than in the deafferented muscle. In the deafferented preparations the "plateau" after-discharge increased in duration more or less in proportion with the duration of the "stimulation" plateau (*364*).

Autogenous inhibition. A common feature observed in the development of crossed extensor reflexes of undeafferented muscles is, as we have seen, a two-step ascent. An initial almost twitch-like step not infrequently occurs which is characterized by a more or less prolonged plateau (see fig. 172 A), and this is followed by a more gradual second step. Now in many records, in which these steps occur, the rhythm of excitatory stimulation, which is usually not clearly visible in the crossed-extensor reflex, becomes evident during the plateau of the first step, growing less marked during the

ascent of the second step (fig. 174). We have seen above that weak inhibitory stimuli applied to an ipsilateral nerve dissect out "the ribs of reflex contraction," *i.e.*, make prominent the rhythm of stimulation through the inhibition of repetitive discharge, and, when applied during the ascent of a contraction, a weak inhibition often prevents the recruitment of additional motoneurones. The two-stepped ascents give every appearance, therefore, of a crossed extensor contraction under slight inhibition, the inhibition commencing *after* the first twitch-like response. This suggests that the muscle has been to a certain extent, self-inhibited by its own contraction. That these two-stepped ascents are to be accounted for by such autogenous inhibition appears likely for the following reasons: (1) they have not, in our

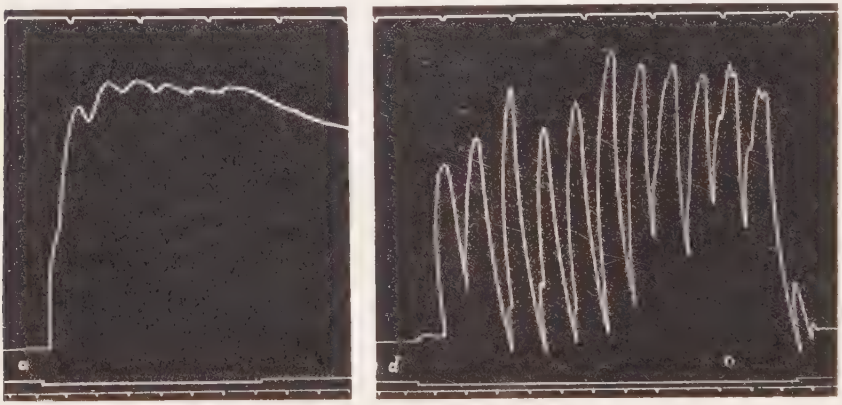

FIG. 175. Isolated vastocrureus (cat); crossed extension reflex excited by a series of break-shocks (lowest signal line) of slow repetition, applied to the popliteal nerve (of opposite limb) during period marked by the signal line lowest but one. *a*, the result in the muscle with normal afferents, *d*, in the deafferented muscle. (Sherrington, *Quart. Journ. Exper. Physiol.*, vol. 2, p. 131, 1909.)

experience, occurred after section of the posterior roots (*e.g.*, fig. 173); (2) as judged by the mechanical record the inhibition commences after an interval of 10 to 30σ and probably somewhat sooner, which is ample time for a reflex inhibition to have become effective; (3) all afferent pain fibres to other regions and muscles of the hind limb have been cut away and therefore the only source of such an ipsilateral inhibition would be the afferent endings within the muscle itself; (4) inhibitory afferents are known to occur in muscle nerves (see above); (5) even when the two-stepped ascent does not occur, the more gradual ascent of the reflex in the undeafferented muscle suggests a similar but less abrupt operation of inhibitory stimuli.

For these reasons it is highly probable that the more gradual ascent of the crossed extensor reflex when the posterior roots are intact is to be explained by progressive slight autogenous inhibition. The more gradual return to the base line of the undeafferented muscle, on the other hand, may be due to the reverse of this, namely, *autogenous contraction* such as occurs in the decerebrate knee-jerk after the cessation of its kinetic phase. It will be recalled that the hump in the relaxation of the jerk has been looked upon as a myotatic appendage resulting from the stretch of inactive fibres ensuant upon the abrupt cessation of the kinetic phase of the knee-jerk. When a group of fibres within a muscle ceases to contract other fibres are stretched by the resulting relaxation. When the incidence of such a stretch falls upon a "stretch afferent" in the muscle it acts as a stimulus and a stretch reflex is in this way evoked. In the case of the crossed extensor contraction recorded under approximately isometric conditions, the assemblage of fibre units cease contracting asynchronously and more or less gradually so that the lengthening will not be great and the incidence of stretch will be correspondingly gradual; therefore the number of stretch afferents affected at any given moment will not be great, but enough presumably are affected to prevent the rapid return to the base line which occurs in the ataxic deafferented muscles. The "shortening reaction," in other words, ensures gradual relaxation, which is so necessary to coördinated movement. The integrity of the proprioceptives also "protects" the muscle from sudden "waves" of inhibition, just as the higher centres appear to protect the spinal centres (see Chapter XIII) from inhibitory stimuli. Sherrington (*919*), for instance, found that any slight disturbance of the animal during the crossed response of the deafferented quadriceps might lead to sudden and complete inhibition of the reflex. Often the inhibition appeared to arise spontaneously.

Liddell and Sherrington (*641*) have pointed out that gradual sigmoid ascents are characteristic of the stepping reflex and that gradual relaxation is similarly characteristic of these movement reflexes, and they have also pointed out (*641*) that recruitment,—both excitatory and inhibitory,—is obviously an important process in the reflex coördination of skeletal movement. It is evident from the above observations that the integrity of the proprioceptive nerves, bringing about as it does a delicate balance between excitatory and inhibitory activity, is an important factor in controlling the gradual character of the recruitment process.

It will be at once obvious from these considerations that the ataxic condition which is at once so striking and so pathetic a feature of *tabes dorsalis*, results from the absence of proper control of the recruitment process both in its excitatory and inhibitory phases (fig. 175).

The observations emphasize further the importance of the *duality* of proprioceptive influence. We have during the *ascent* of a crossed extensor reflex the operation of proprioceptive inhibitory fibres ("lengthening reaction"), and it seems legitimate to infer that contraction *per se* is an adequate stimulus for these inhibitory fibres. In the period of relaxation, both of the crossed extension reflex and of the knee-jerk, one also has the evidence of the activity of the proprioceptive excitatory afferents leading to the "shortening reaction." From the observations on the stretch reflex it has been inferred that the mechanical stretch is the adequate stimulus for these end-organs.

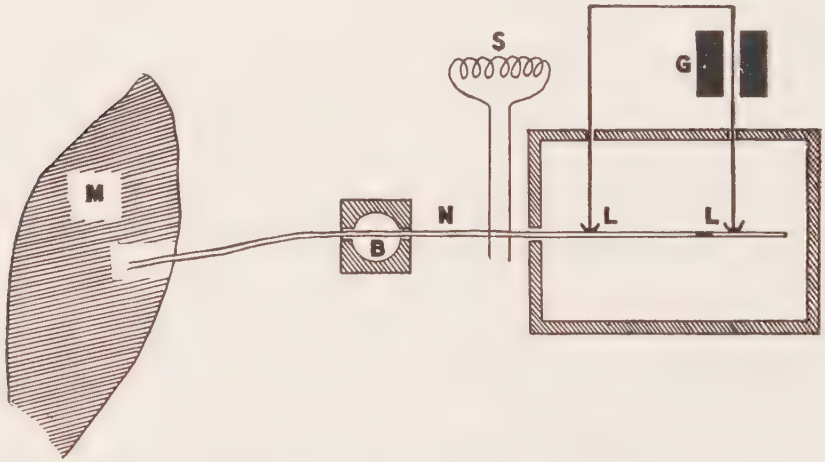

FIG. 176. Diagram of an arrangement for recording monophasic proprioceptive action currents, with alcohol block control. *S*, secondary coil of stimulating inductorium; *G*, galvanometer; *N*, nerve, *M*, muscle, *LI*, leading-off electrodes; *B*, alcohol narcotizing chamber. (Forbes, Campbell and Williams, *Amer. Journ. Physiol.*, vol. 69, p. 286, 1924.)

Action currents of proprioceptive nerve impulses. The existence within muscle of two functionally different groups of centripetal (proprioceptive) fibre suggests a possible explanation of the interesting results obtained by Forbes, Campbell and Williams (*328*). They observed that when the tibialis anticus muscle is stimulated indirectly by a single break-shock, and amplified electrical responses (monophasic) are obtained from the motor nerve (peroneal), there occurs first a large excursion set up by the volley of motor nerve impulses; and this is followed in turn by two secondary excursions, which are of proprioceptive origin, since they disappear when an alcohol block is applied to the nerve between the leading-off electrodes and

the muscle (fig. 176). Galvanometer records from their experiments are shown in figure 177, and their results are shown diagrammatically in figure 178. Now, the first excursion of the proprioceptive complex (*b* and *c*) occurs at an interval of 10 to 15σ after the stimulus, while the second excursion of the complex (*d*) falls after an interval varying from 60 to

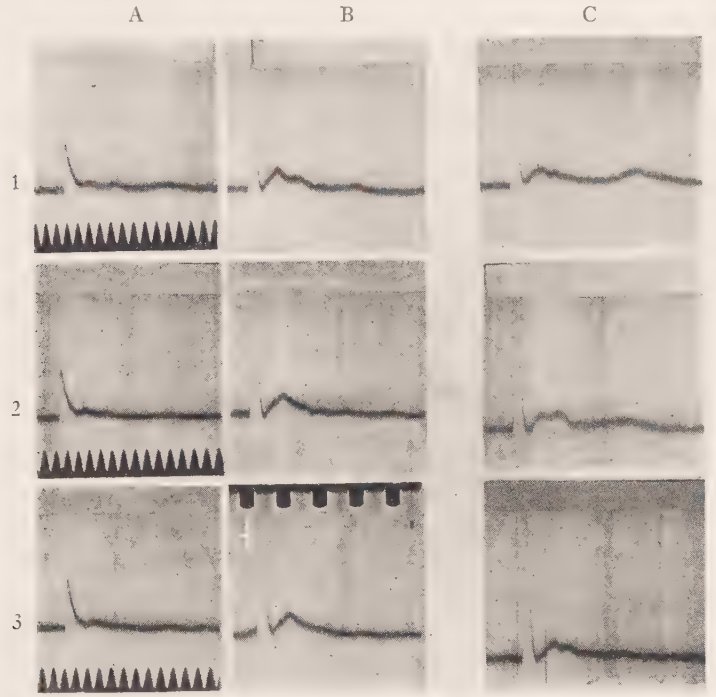

FIG. 177. Records showing the effect on proprioceptive impulses (tiabilis anticus, cat) of varying the limitation of flexion in response to electric stimulation of motor nerve. (1) Little or no limitation; (2) medium limitation; (3) extreme limitation. Speed of film 16 cm. per second.

A. Unaided galvanometer string.

B. Same string as in A, but with electron-tube amplification.

C. The same as in B. (Forbes, Campbell and Williams, *Amer. Journ. Physiol.*, vol. 69, p. 297, 1924.)

145σ. They suggest that the *bc* complex is associated with the development of tension in the muscle, but leave as problematical the significance of the second complex (*d*). They made the important observation, however, that the *d* wave tends to disappear if the shortening of the muscle was restricted by fixating the ankle-joint, *i.e.*, when the conditions of contraction

are made more nearly isometric. The interval at which the *d* wave occurs is approximately that elapsing between the beginning of a twitch and half-relaxation. Thus, if the duration of the twitch measured to the "angle" is 45σ, "half-relaxation" will occur at bout 60σ in the case of an isometric twitch. When, however, as in Forbes, Campbell and Williams' experiments, relaxation is brought about through the weight of the pendant ankle, there will clearly be some lag before the muscle reaches a point of half-relaxation. This being the case, the observed interval of 60 to 145σ falls within the expected limits if the *d* complex owes its existence to proprioceptive impulses set up by the relaxation (lengthening) of the muscle.

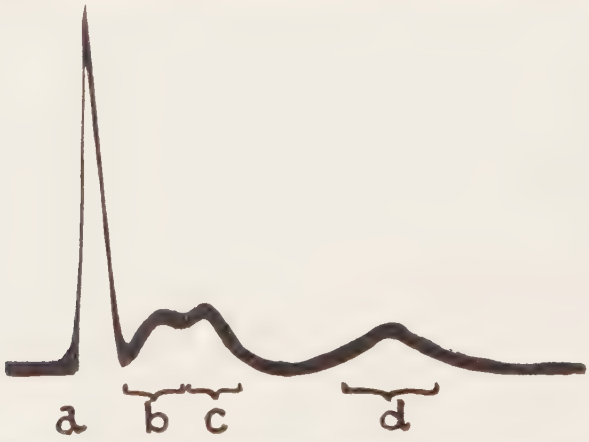

FIG. 178. Diagram of typical monophasic record for identification of characteristic excursions. *a*. is the direct motor nerve response, *bc*, the proprioceptive impulses elicited by the active contraction *d*, which is of diminished size when the muscle cannot shorten. (Forbes, Campbell and Williams, *Amer. Journ. Physiol.*, vol. 69, p. 297, 1924.)

We have seen in the case of the decerebrate knee-jerk that relaxation sets up a proprioceptive reflex giving rise to the so-called "myotatic" appendage. When a muscle relaxes, or in other words, when tension is applied which leads to lengthening, stretch afferents are stimulated and the stretch reflex is in this way elicited. When, however, a muscle contracts suddenly, leading to the abrupt development of tensile strain, the nociceptive (or "pain") afferents appear to be stimulated; in the case of a reflex response (*e.g.*, crossed extensor) this causes a mild degree of reflex inhibition which leads to a less rapid mechanical ascent of the response (fig. 174). It is therefore reasonable to look upon the *bc* complex in Forbes, Campbell and Williams' experiment as due to proprioceptive stimulation in which inhibi-

tory centripetal impulses predominate. We have already discussed the question of the adequate stimulus for the various forms of proprioceptive afferent impulses (Chapter XV), and rather than err in the direction of being too specific as to the exact nature of the mechanical stimulus, it can be said that any circumstances leading to unduly severe tensile strain, such as that caused by sudden contraction of a muscle recording isometrically, leads to the stimulation of inhibitory proprioceptive afferents. Slight degrees of stretch, on the other hand, such as are produced by passively lengthening a tonic muscle, appear to set up impulses which lead to reflex contraction, *i.e.*, to stimulation of "stretch" afferents.

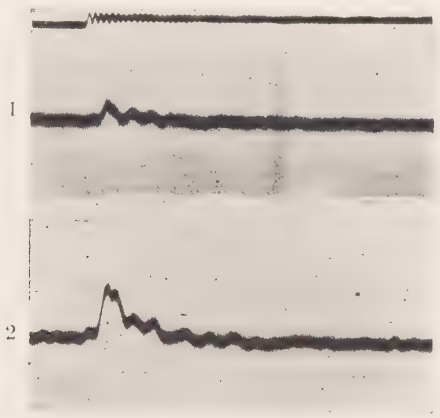

FIG. 179. Records showing responses of afferent fibres in the peroneal nerve when the tibialis anticus muscle is suddenly stretched. Electron-tube amplification with 0.3 microfarad condenser damping. Speed of film 19 cm. per second.

(1) Diphasic response; (2) monophasic response. Nerve was crushed between leads after *1* and before *2*. No other change in set-up. (Forbes, Campbell and Williams, *Amer. Journ. Physiol.*, vol. 69, p. 291, 1924.)

Forbes, Campbell and Williams also were able to detect proprioceptive impulses in the nerve when the inactive muscle was quickly stretched (see Chapter XV). Their record demonstrating this is given in figure 179. Forbes, Campbell and Williams' experiments have lately been confirmed and extended by G. P. McCouch and Forbes (unpublished).

SUMMARY

When, in a decerebrate preparation, the leg is forcibly flexed, an observer encounters at first considerable resistance, which, under continued pressure, suddenly gives way and the leg may then be carried to a position of extreme

flexion. This constitutes the "lengthening reaction." If, however, the passive manipulation is carried only a short distance after the "lengthening reaction" has been elicited, resistance is once more encountered when attempting to move the limb still further. When the leg is passively extended, it is found, owing to activity of the quadriceps muscle, that the leg will remain in any position to which it may be carried. This, then, is the "shortening reaction."

The "lengthening reaction" is due to a reflex inhibition, the adequate stimulus being the severe tensile stress necessary for its elicitation. It is a proprioceptive reflex and may be obtained after complete denervation of all structures in the limb except the one nerve passing to the quadriceps muscle. Arguments are brought forward to show that the "lengthening reaction" is due to stimulation of nociceptive endings within the muscle. The elicitation of the "lengthening reaction" is always accompanied by a crossed extension reflex (Philippson's reflex), as well as ipsilateral flexor contraction.

The "shortening reaction" is a manifestation of the stretch reflex, the adequate stimulus being any slight passive tensile force applied to the muscle along its longitudinal axis. In the presence of *severe* stress, however, the proprioceptive inhibitors are stimulated, and these overcome the effect of the stretch afferents and give rise to the "lengthening reaction." Delicate muscular coördination depends for its existence upon the integration by the central nervous system of these two opposed proprioceptive reflexes.

Evidence of the operation of both types of proprioceptive influence is to be seen in the record of any crossed extensor reflex. In the *undeafferented* muscle, the rise of tension is gradual, seldom reaching a well-defined plateau, since the "plateau" usually tends to climb. The duration of the plateau after-discharge is usually less pronounced than in a deafferented limb, but the curve of relaxation is gradual and prolonged. In a *deafferented* muscle, on the other hand, the crossed extensor reflex rises abruptly and quickly reaches its plateau; after cessation of stimulation there occurs a more or less prolonged plateau after-discharge which terminates suddenly, and a rapid relaxation ensues. These differences have been interpreted as indicating that in the "normal" muscle the rise in tension leads to the gradual operation of autogenous inhibition; and, similarly, that the more gradual relaxation is an expression of autogenous contraction, *i.e.*, of an appended stretch reflex, the result being a more coördinated response in which abrupt, and therefore dangerous, alterations in contraction tensions are avoided. The *dual* influence of the proprioceptive nerves is therefore once more emphasized.

CHAPTER XVIII

The Coördination of Antagonistic Muscles: Reciprocal Innervation

In the interest of coördination and economy it is essential that antagonistic muscles shall not work against each other in the performance of a given movement. However this may be, many writers have observed that under some circumstances antagonistic muscles apparently do contract simultaneously in opposition to each other, and it is for us to enquire under what circumstances this occurs and for what reason.

Our knowledge concerning the functional activity of antagonistic muscles had its origin early in the observations of Galen (*373*). He introduced the view that when a muscle contracts, its antagonist remains dormant.[1] It is interesting to find that in 1662 Descartes (*234*) suggested, in discussing the eye muscles, that when the external rectus muscle contracts to produce lateral rotation, the internal rectus simultaneously relaxes. He postulated the existence of a valvular mechanism whereby vital spirits were transferred from one muscle to the other, *i.e.*, he imagined the mechanism to be peripheral instead of central. In the eighteenth century Haller (*Elementa Physiol.*, Lib. xi, Sec. II, par. xlii, pp. 506–509) discussed all views concerning the functional relations of antagonistic muscles which had been expressed before his time, and concluded that a conception similar to that of Galen was nearest the truth. Winslow (1732, *1058*) added to the controversy by introducing the view that antagonistic muscles may contract concurrently but that the contraction of the antagonist occurred merely in order to offer a "moderating resistance." Winslow called the antagonists the "moderators" and he believed the resistance offered by the weight which

[1] One of Galen's (numerous) observations on this subject may be translated as follows: "The contracting muscle therefore draws itself up and at the same time the relaxed muscle becomes extended; on this account both muscles are moved in a direction appropriate to each. But the process is this: the stimulated muscle [*i.e.*, the "prime mover"] contracts of itself independently of the other. Accordingly the muscle already in action affects the other passive muscle as if it were a part of the member being moved." This occurs in the *De Motu Musculorum*, Bk. I, Ch. IV (not in the *De Usu Partium*, as has been stated, *988*), and is to be found in Vol. 2, p. 331, of Daremberg's French translation (*373*). The above selection is taken from the Leonicenus Latin text.

was being lifted might in itself serve as a sufficient moderating force and in this way compensate for any existing deficiency of contraction of the "moderators." This conception became widely accepted, and it was extended and modified by the observations of Duchenne of Boulogne (*249*). It was this investigator who employed the somewhat paradoxical term "harmonie des antagonistes." He asserted that in muscles executing voluntary contraction the flexors and extensors often give evidence to palpation of simultaneous contraction. From this Duchenne concluded that an important factor in the coördination of movement was the simultaneous contraction of antagonistic muscles in order that the moving joint may at all times have an adequate stabilizing force. He states, for instance, "This nervous action causes, on the one hand, the contractions of the muscles which produce these motions, and on the other, the immediate and parallel contraction of the muscles called antagonists which modify and stabilize them." In the course of the nineteenth century this question was frequently debated, and as a detailed historical account of the controversy has been recently published by Tilney and Pike (*373*) we need not stop to consider it here. It is sufficient to say that both Sir Charles Bell (*67*) and Pettigrew (*767*) refused to accept the view of simultaneous contraction of antagonists chiefly on the grounds of the unnecessary wasting of energy which such a process would demand. Brücke (*170*), Beaunis (*62*), and Demeny (*232*), on the other hand, maintained the view put forward by Duchenne.

RECIPROCAL INNERVATION

New light was thrown on the question by Sherrington's exhaustive researches[2] on the functional relations of antagonistic muscles, the outcome

[2] Sherrington's chief investigations on reciprocal innervation are contained in a series of fourteen communications which appeared in the *Proceedings of the Royal Society* between 1893 and 1909. As some of the early volumes of the *Proceedings* are difficult of access it may be useful to review briefly the contents of these communications. The *first* note (*875*) dealt with the antagonistic relation between the extensors and the flexors in the knee-jerk. He found that massaging the flexor tended to inhibit the jerk of the extensor, and that stimulation of the central cut end of the hamstring nerve served to inhibit the knee-jerk completely. The *second* note (*877*) was concerned with the reciprocal correlation of the antagonistic eye muscles; he found that after cutting of the third and fourth nerves the external rectus muscle (innervated by the sixth) relaxed when the gaze was directed in such a way as to oppose its action, and it could be made either to contract or to relax by cortical stimulation (see p. 452 below; also, *166*). In the *third* communication (*882*) decerebrate rigidity was described for the first time and it was shown that ipsilateral afferent stimulation caused relaxation of the extensors and contraction of the flexors of the hind limb. The *fourth* note (*887*), by Sherrington and Hering, drew

of which was the enunciation of the law of "reciprocal innervation." It is important at the outset to define as simply as possible precisely what is implied by this term, for several authors appear to have misconstrued both the original conception of reciprocal innervation as well as its functional significance, and they have been led on somewhat uncertain evidence to deny the existence of this important feature of reflex coördination. Experiment has shown that when a decerebrate or spinal preparation executes a muscular movement, *augmentation of contraction never proceeds concurrently in antagonistic muscles, and similarly diminution of contraction in antagonists does not occur concomitantly.* The conception of reciprocal innervation does not, however, imply that antagonistic muscles are never in a state of contraction at the same time. It merely states that *increase* of contraction (or the converse) does not proceed simultaneously in opposed muscles. By this is meant that as contraction progresses in a muscle (*e.g.*, an extensor), contractile activity diminishes *pari passu* in the antagonistic flexor. Contraction *may* thus be present simultaneously in two antagonistic muscles but in a reciprocal relation. Briefly, but rather

attention to the fact that movements of the extremities evoked either by cortical stimulation or by stimulation of the internal capsule was characterized by reciprocal activity of the muscle groups involved. Extensor and flexor groups of both the fore and hind limbs were examined. The *fifth* contribution (*890*) directed attention to the fact that there is a reciprocal relation between the activity of the levator palpebrae superioris and the obicularis palpebrarum. In the *sixth* note (*893*) it was shown that certain hind limb reflexes in the frog are characterized by reciprocal innervation and that the reciprocal relation continues to exist after complete removal of the skin. In the *seventh* contribution (*905*), in which the phenomenon of a successive spinal induction was described, it was shown that the antagonistic centres were affected reciprocally by this process. The *eighth* note (*906*) contained a detailed account of the activities of all muscles involved in moving the knee joint, and the reciprocal activity of each of the antagonists was carefully analyzed. In the *ninth* communication (*907*) the so-called "mark-time" reflex of the spinal dog were described and further observations were given on the phenomenon of successive spinal induction. The *tenth* note (*911*) contains a series of more general observations on the reciprocal activity of the muscles in the hind limb, and among other things it is pointed out that the muscles which are inhibited in ipsilateral stimulation are those which are concerned in counteracting gravity (*i.e.*, maintaining the animal in an erect position). The *eleventh* note (*914*), as the title indicates, contains further observations on successive induction. In the *twelfth* note (*915*) is described for the first time, the so-called "lengthening" and "shortening" reactions (Chapter XVII) characteristic of the extensor muscles in decerebrate rigidity. In the *thirteenth* communication (*916*) it is shown that when inhibitory and excitatory stimuli converge simultaneously upon the same motor centre, algebraical summation is the result. Finally, in the *fourteenth* contribution (*918*) the analysis of double reciprocal innervation, which is discussed on page 455 of this monograph, was described in detail.

inaccurately, if the extensor muscle is contracted to $\frac{9}{10}$ of its maximum the opposing flexor may be contracted only to $\frac{1}{10}$ of its fullest extent. By this reciprocal arrangement steadiness of movement is obtained without antagonism. For convenience we may term the muscle which contracts the "protagonist" or "prime mover," and the muscle which relaxes the "antagonist."

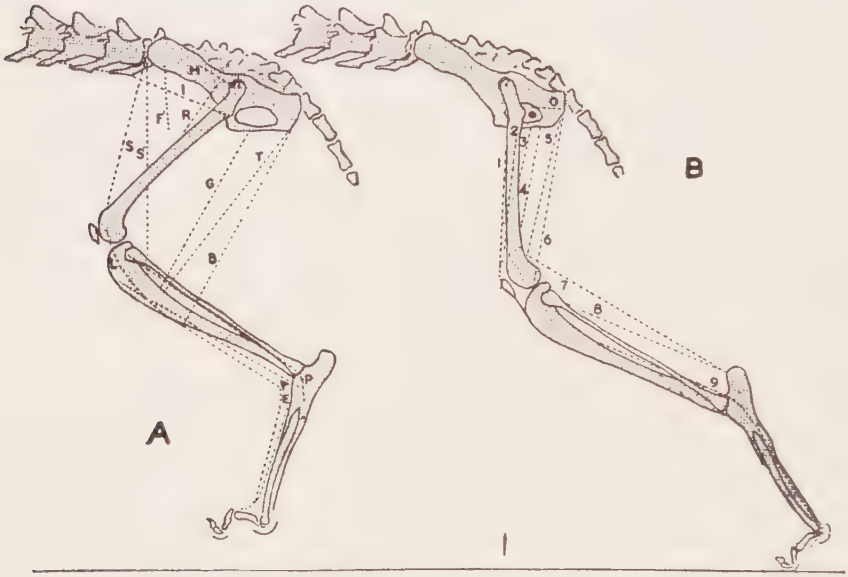

FIG. 180. Figure illustrating the muscles actually observed by experimental analysis to be engaged in contracting in the flexion-phase (A) and in the extension-phase (B) of the reflex step of the cat. Those which contract in the flexion-phase are relaxed by inhibition in the extension-phase, and conversely.

A. A, tibialis anticus; B, biceps femoris posterior; E, extensor brevis digitorum; F, tensor fasciae femoris; G, gracilis; I, psoas; L, extensor longus digitorum; M, gluteus minimus; P, peroneus longus; R, rectus femoris; S, sartorius lateralis; S′, sartorius medialis; T, semitendinosus.

B. O, quadratus femoris; 1, crureus; 2, vasti; 3, adductor minor; 4, adductor major (a part); 5, semimembranosus; 6, biceps femoris anterior; 7, gastrocnemius; 8, soleus; 9, flexor longus digitorum. (Sherrington, *Quart. Journ. Exper. Physiol.*, vol. 6, p. 260, 1913.)

Reciprocal innervation has been studied under a large variety of conditions. To facilitate textual description they may be divided into three groups: (1) The study of the behaviour of antagonistic muscles of a spinal or decerebrate preparation when responding to simple reflexes such as the flexor reflex, crossed extensor reflex or scratch reflex; (2) the response of

antagonistic muscles to stimulation of the motor area of the cerebral cortex; (3) the behaviour of antagonistic muscles of an intact animal during voluntary contraction.

Reciprocal innervation as studied in simple reflexes. The most extensive investigations on reciprocal innervation have been conducted upon the musculature of the hind limb of dogs and cats. It is essential, therefore, to have some idea as to the arrangement of the antagonistic muscles in this limb. As is well known, they fall into the two groups of flexors and extensors. When the flexor reflex is evoked the following muscles contract more or less actively (*920, 921*):

Iliopsoas	Gracilis
Pectineus (slight)	Semitendinosus
Sartorius (?) slight, part inserted into patella	Biceps femoris posterior
Tensor fasciae femoris (weak)	Tenuissimus
Rectus femoris (?) weakly	Tibialis anticus
Gluteus minor	Peroneus longus
	Extensor longus digitorum

These muscles are shown diagrammatically in figure 180. They are all examples of *synergic* muscles, *i.e.*, muscles which act in the same direction mechanically at the same joint, or which act similarly at two neighbouring joints, as by flexing or extending the hip or knee. This is referred to as "identical innervation" in contrast to reciprocal innervation. The muscles which relax during the flexor reflex (or merely remain passive) are shown in the following list.

Vastus lateralis	Biceps femoris anticus
Vastus medialis	Flexor longus digitorum
Crureus	Quadratus femoris
Gastrocnemius	Adductor minor
Soleus	Adductor magnus
Semimembranosus	Rectus femoris

Thus, when an ipsilateral afferent nerve of the hind limb is stimulated the flexor muscles indicated in the first list above contract, and the extensor muscles indicated in the second list relax. Thus when the responses of *any pair* of antagonistic muscles indicated in the two tables are recorded simultaneously by a double myograph, the result is decisive. A typical record of such an experiment is shown in figure 181. It may be urged, however, that the operative procedure necessary for the myographic examination in such an experiment is so unnatural as to vitiate any conclusions. When, however, the muscles are allowed to remain intact, and the flexor reflex is evoked by pricking the pad of the foot, it is obvious to

palpation that the flexors have contracted and the extensors relaxed; consequently the circumstance of their tendons being isolated offers no real objection to results of the experiment (cf. G. McCouch, *703*).

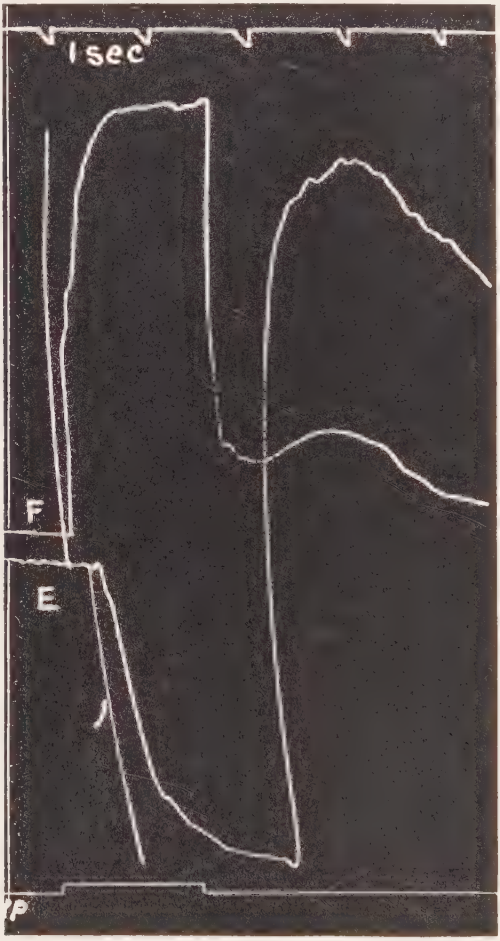

FIG. 181. Reciprocal reflex of antagonistic muscles of knee. F, semitendinosus, a knee-flexor; E, vastocrureus, a knee-extensor. IP, ipsilateral popliteal nerve. The inhibition of the extensor is followed by marked rebound contraction, which is accompanied by a simultaneous relaxation of the flexor muscle. Decerebrate cat. Time marked above in seconds. The signal line signals upward. The myograph writer for extensor muscle is set a little to right of that for flexor muscle, in order that the two may clear each other: the ascent of F and the descent of E are therefore, in fact, practically synchronous. (Sherrington, *Quart. Journ. Exper. Physiol.*, vol. 6, p. 257, 1913.)

The converse condition obtains when the crossed extensor reflex is elicited. Stimulation of a contralateral afferent nerve causes contraction of the extensor group and relaxation of the flexors. In this case the extensors are the protagonists and the flexors are the antagonists. In both the crossed extensor and the flexor reflexes the extent of the contraction of the protagonists and the extent of the relaxation of the antagonists exhibits reciprocally delicate gradation of response as the strength of stimulation is varied. This is true whether a stimulus be artificial (*i.e.*, a series of induction shocks applied to a bared afferent nerve) or natural (*i.e.*, pinching or pricking the pad of the foot), and whether a decerebrate or a spinal preparation is used. Consequently there is no reason for believing that it is not also true of the intact animal. As evidence of this one may examine the scratch reflex.

As is well known, the *scratch reflex* occurs in the intact animal (*908*). The passage of a flea through the fur or the bite of such a parasite is sufficient in many mammals to provoke a purposive rhythmic movement of the hind limb directed toward the extermination of the invading pest. The reflex is, of course, under the control of the will and the animal can inhibit the natural operation of the rhythmic movements by means of its own volition. Moreover, when an animal is made "spinal" by transecting the cord aseptically in the thoracic region and allowed to recover, the scratch reflex may still be elicited, but it is not then subject to voluntary inhibition. Graham Brown (*159*) demonstrated by the use of a double myograph that reciprocal innervation clearly holds in the case of the scratch reflex. Thus, when the protagonist extensor muscle contracts bringing the limb forward to the site of stimulation, the antagonistic flexor relaxes so as to permit of the rapid and delicately coördinated performance of the rhythmic act. In this instance, therefore, we have a clear-cut example of a reflex which occurs both in the intact and in the spinal animal; in the latter condition reciprocal innervation clearly obtains and consequently we have every reason to believe that it obtains similarly in the normal animal.

The instances in which reciprocal innervation has been observed might be multiplied indefinitely. A large number of examples is, for instance, to be found in Magnus's (*679*) exhaustive study of animal posture. The examples just cited, however, will give to the unbiased observer clear evidence that in the case of the spinal and decerebrate reflexes at least, the plan of the central nervous connections is such that concurrent contraction of antagonistic muscles can only occur in simple reciprocal relation. Increase of contraction in one is invariably associated with diminution of contraction in another, and this is true whether the stimulus be natural or artificial—a flea bite or an electrical shock.

Cortical stimulation. The muscular responses to cortical stimulation have been exhaustively studied in dogs, cats, and in the higher apes. When an appropriate portion of the motor cortex (or the internal capsule, *887*) of one of these animals is stimulated, various parts of the appendicular skeleton may be made to respond according to the particular region of the cortex to which the stimulus is applied. If, for instance, the hip-joint is flexed the extensors of the hip are observed to be relaxed, and similarly if the knee-joint is flexed the quadriceps and other muscles in the extensor group become *ipso facto* inhibited. An interesting feature of cortical stimulation is that the inhibition produced thereby is often far more extensive than the contraction. Thus, to move the first finger of a monkey the intensity of stimulation was in one experiment increased to such an extent that the deltoid and other muscles in the shoulder and forearm of the same limb underwent extensive relaxation. A similar phenomenon has often been observed in the hind limb. To move the ankle one frequently observes that the extensors of the knee and hip are inhibited. This may possibly be accounted for by the fact that the condition of light anesthesia necessary for the performance of this experiment favours the inhibitory process and tends to depress excitatory effects.

Prolonged stimulation of the cortex not infrequently gives rise to localized epileptiform convulsions of various portions of the musculature, and, as in typical Jacksonian epilepsy, the convulsion may occur simultaneously in antagonistic muscles. This, however, does not necessarily offer an objection to the previous inferences but merely suggests that owing to the local irritation set up by the persistence of the exciting stimulus, the volleys of impulses sent out are so intense as to break down the spinal mechanism of reciprocal innervation. It may be recalled that stimulation of the cortex causes a local blanching of the brain substance surrounding the electrode (Sherrington, *633*). Of interest in this connection is Florey's (*311*) recent observation that on stimulation of the cortex small bubbles of gas are to be seen (binoculors) rising from beneath the stigmatic electrode. This shows the extent of the disturbance which is caused by such a procedure. In keeping with this Vogt und Vogt (p. 71, Taf. 12[3]) have found that cortical stimulation may lead to extensive degeneration of cortical neurones beneath the spot stimulated.

An interesting observation made by Graham Brown and Sherrington (*167*) is that when two cortical points antagonistic to each other are stimu-

[3] Vogt, C. und O. Vogt. "Erkrankungen der Grosshirnrinde in Lichte der Topistik Pathoklise und Pathoarchitektonik." Journ. f. Psychol. u. Neurol., Bd. 28, pp. 1–171, 112 Taf.

lated concurrently there results an algebraical summation of the two effects. Thus, if a point A, which produces flexor contraction is stimulated simultaneously with a point B, which produces flexor relaxation, the result will be a delicate algebraical balance of effect. There are many reasons, which will be presently alluded to, for believing that in a normal animal delicate gradation of voluntary contraction is obtained by the simultaneous interplay of excitatory and inhibitory effects,—in other words, algebraical summation.

Voluntary contraction. The analysis of voluntary contraction is beset by many difficulties, not the least of which is the uncertainty and the idiosyncrasies of the volitional process itself. Many writers in the past have observed that certain movements are associated with an obvious contraction of the protagonist and a palpable relaxation of the antagonist. Thus Beevor (*66*) has observed that if a subject contracts his biceps in such a way as to lift a weight, the muscles on the dorsal surface of the forearm become more or less flabby while the biceps itself becomes rigid. In this instance, therefore, it would seem that the mechanism of reciprocal innervation was in operation. Nevertheless, one may very readily contract both extensors and flexors simultaneously and so produce a condition of rigidity in all muscles concerned. Consequently experiments on voluntary contraction have yielded most divergent results and one is led to suspect that the cause of the divergence is largely due to voluntary control. Another important consideration, however, is the instrumental difficulty of estimating intrinsic contractile tensions in the intact animal. Because of this a large number of indirect methods have been employed, such as tambours, phonograms and electromyograms, and the results are often obscure and difficult of interpretation. The majority of investigators, however, place more reliance upon the experiments performed on chronic spinal and decerebrate animals in which the tension relations of antagonistic muscles are directly measurable. Here reciprocal innervation obtains undeniably, and the presence or absence of a cortex in all probability does not modify this fundamental plan of reflex organization.

Despite the convincing nature of the evidence provided by Sherrington, Graham Brown and others, several recent workers have concluded that the condition of reciprocal innervation does not obtain in normal voluntary movement. Before considering their experiments a few words may be said concerning double reciprocal innervation.

Double reciprocal innervation. When two afferent nerves, one of which causes flexor contraction and extensor relaxation, the other causing the converse of this,—flexor relaxation and extensor contraction,—are stimu-

lated simultaneously, the strength of the respective stimuli may be so adjusted that contraction occurs in both flexor and extensor muscles without

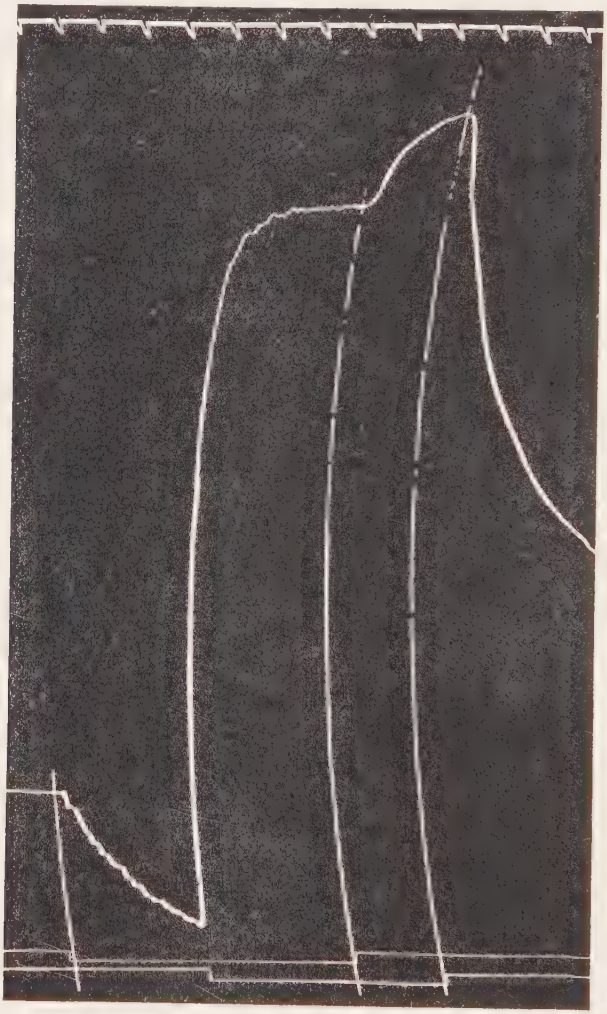

FIG. 182. Algebraic summation. Reflex reaction of vastocrureus muscle under, at first, the influence of an inhibitory afferent nerve (upper signal line); then the conjoint influence of that nerve and of an excitatory afferent (lower signal line) concurrently stimulated; and, finally, the influence of the excitatory afferent alone. The observation illustrates the algebraic summation of the two opposed influences. The excitatory afferent was contralateral popliteal nerve, the inhibitory, ipsilateral popliteal. Decerebrate cat. Time above in seconds. (Sherrington, *Proc. Roy. Soc.*, vol. 80B, p. 572, 1908.)

movement. By slightly altering the relative strength of stimuli either the flexor contraction or the extensor contraction may be made to predominate. A little reflection will make it apparent that what actually occurs under these circumstances is an algebraical summation of reflex effect in both the extensor and the flexor centres (fig. 182). Thus, of the two afferent nerves simultaneously stimulated, the one which when stimulated alone causes *flexion* of the joint, *excites* the flexor "half-centre" and *inhibits* the extensor "half-centre;" the other afferent, which when stimulated alone causes *extension* of the joint, *excites* the extensor "half-centre" and *inhibits* that of the flexor. Both centres, in other words, are subjected to algebraical summation. It is this condition which Sherrington (*918*) has termed "double reciprocal innervation." The importance of the condition in normal reflex coördination is best illustrated by the following quotation.

"The simple reciprocal innervation described above must be regarded as probably a relatively artificial reaction, because the experimental conditions under which it is produced are not merely more crudely produced but much less complex than are natural happenings. The isolated stimulation of just one whole afferent nerve, the rest of the nervous system lying plunged at the time in approximately complete quietude, is a state of things little resembling the ordinary occurrences of waking life. Usually in the latter the reactions of the nervous system result from the combination of a number of stimuli playing concurrently on its afferent channels, some impelling to one action and some to another. Any particular motor centre, whether for flexion or extension, lies then under at least a twofold influence, tending on the one hand toward excitation and on the other toward inhibition. Such twofold influence can be imitated and its reflex results studied, in an elementary way at least, by taking a pair of antagonistic muscles and two afferent nerves, the one nerve exerting an opposite reflex effect to the other upon the muscle-pair in question" (*925*, p. 268–269).

Pseudo-antagonistic muscles. It was observed by Hering (*460*) that in grasping an object with the hand (*i.e.*, in flexing the digits), the extensors of the hand contracted as well as the flexors. But Hering pointed out that the extensors digitorum not only tend to extend the digits but they have the important subsidiary action of extending the wrist joint. In order to grasp an object it is of course absolutely essential that the wrist joint remain more or less fixed. Consequently, the contraction of the extensors of the digits under these circumstances cannot be looked upon as a true antagonism because it is a very real assistance in the performance of the flexor digitorum contraction. It was on account of this circumstance that Hering (*460*) gave to the extensors digitorum and other muscles which act similarly the somewhat unhappy term "pseudo-antagonist." Examples of pseudo-antagonists are to be found also in the hip and knee joints, and while they are clearly of importance in the coördination of movement they do not

affect in any way the fundamental fact of reciprocal innervation. The other apparent exceptions to the general law of reciprocal innervation have been discussed at length by Sherrington (*921*, pp. 47–52). Other instances of pseudo-antagonism,—joint fixators,—have recently been described by Magnus (*681*) in his study of the supporting reaction of thalamic animals.

OBJECTIONS TO THE LAW OF RECIPROCAL INNERVATION

Recently Golla and Hettwer (*402*, *403*) have obtained simultaneous electromyograms of the flexor and extensor muscles during certain simple voluntary movements. They inserted two gilded pins in each of the muscles to be examined and these were led off to an Einthoven galvanometer. As a control to the electrical response these authors also obtained electrophonograms during activity of the antagonistic muscles. They examined in man such antagonistic muscle groups as the anterior tibial and gastrocnemius, the biceps and triceps, and quadriceps and the flexors. When a voluntary movement was performed they found that action currents tended to occur simultaneously in both protagonists and antagonists. Usually it occurred in the protagonist somewhat earlier than in the antagonist. The muscle sounds tended to behave in exactly the same way. When these results were communicated to the Neurological Section of the Royal Society of Medicine it was believed that they provided a fundamental objection to the classical conception of reciprocal innervation, but in the published results this direct implication is carefully avoided. Walshe (*1025*) has pointed out, however, that electrical responses recorded in this way are notoriously subject to adventitious disturbance. The movement, for instance, of the connective tissue and the underlying muscles against the skin would be sufficient to set up a large electrical disturbance, and those who have taken galvanometer readings from contracting muscle are familiar with this danger (p. 415). Under the circumstances of these experiments, therefore, an electrical deflection might occur whether the muscle contracted or whether it relaxed, provided only the alteration in its condition gave rise to a movement under the connective tissue and skin. Also the possibility of spreading of electrical effect from active muscle groups to those which are inactive is an ever present difficulty. Moreover, even if the electrical responses were genuine it is not infrequently the case that large electrical responses are observed in a muscle when it is being inhibited (see *364*). The results obtained with the phonogram are somewhat more satisfactory, but even here critics might contend that the internal friction set up by muscular relaxation would give rise to muscle sounds of as much consequence as those set up by the friction attendant upon contraction. It may be emphasized that muscle sounds are not due inherently to the contractile process itself but to the *rubbing incident upon contraction, and internal frictional disturbances occur during relaxation as well as during contraction.* These objections, however, do not completely invalidate the conclusions of Golla and Hettwer, for we have already found evidence that in voluntary movements extensors and flexors are often provoked into contraction concurrently in highly integrated responses, and the experimental procedure of these investigators does not rule out the possibility that this occurred in their experiments. Wachholder (*1005-1010*), Pfahl (*769*) and Wagener (*1012*) have recently reported similar experiments which, though more carefully controlled than those of Golla and Hettwer, are nevertheless open to similar criticism.

Recently (1925), Tilney and Pike (*988*) have published a series of observations which purport to prove that Sherrington's conception of reciprocal innervation is wholly inadequate and that the older view of Duchenne (*249*) and Beaunis (*62*) of "synergic co-contraction" of anatomically antagonistic muscles must be reinstituted. The experimental evidence upon which these conclusions rest is somewhat as follows: They performed (independently) Golla and Hettwer's experiments, using in place of their technique a series of tambours by means of which the rigidity of flexor and extensor muscles are synchronously recorded. They find that during voluntary movement the "tension" of antagonistic muscles, as inferred from tambour tracings, increases *pari passu*, in most instances. In some, however, they observe the converse of this, *i.e.*, reciprocal innervation ("contraction-relaxation phenomenon"). Their experiments are open to the objections already mentioned, namely, that in the highly integrated (voluntary) responses, one *may* and often does find simultaneous contraction of antagonists. Their other experiments consisted in a repetition of cortical stimulation, and in these they obtained evidence of synchronous co-contraction, using tibialis anticus and gastrocnemius as "antagonists." They lay particular emphasis upon the experiments in which they apparently obtained synchronous co-contraction, but they fail to direct attention to the fact that Sherrington (*921, 925*) and Graham Brown and Sherrington (*167*) frequently obtained the same thing.

The essence of the idea of integration is that simple reflexes are built up to form complex reactions, and this obviously allows the highly integrated reflex to differ from the simple. Reciprocal innervation is the rule in the cord, but under some circumstances "co-contraction" occurs in the intact animal; both are observed facts and not possible explanations. That reciprocal innervation should not always obtain in cortical stimulation, is scarcely a matter for surprise in view of the conditions necessary for carrying out the experiment.

Tilney and Pike (*988*) discuss very fairly the possible objections which may be raised to the interpretations placed upon their experiments. They state that they at first attempted to look upon them in the light of reciprocal innervation, but that their persistent observation of synchronous co-contraction in response to cortical stimulation rendered the Sherringtonian interpretation, in their opinion, untenable. They suggest that critics may look upon their experimental results as due to the contraction of pseudo-antagonists. They, however, fail to meet this objection, which is certainly an important one, and merely emphasize the inadequacy of "pseudo-antagonist" as a descriptive term. One should also take into consideration the fact that antagonistic muscles can be made to contract simultaneously by voluntary effort. This being the case, it is not surprising that under some circumstances cortical stimulation leads to concurrent contraction of antagonists. It is unfortunate that these authors did not extend their observations to the classic examples of antagonism, *i.e.*, the flexors and extensors of the knee joint. Gastrocnemius and tibialis, though generally regarded as anatomical antagonists, are not as directly antagonistic in their action as for instance vastocrureus and semitendinosus, for tibialis in addition to flexing the ankle joint inverts the foot.

Tilney and Pike (*988*) also discuss experiments on eye muscles and they interpret the observations which have been made in the past as contrary to the law of reciprocal innervation. They believe that the operative procedure necessary to examine the tension relation to the muscles directly is so severe as to vitiate any conclusions which might be drawn from such experiments. But in addition to this they object to such inferences as have

been drawn from analyses of movements of the intact eye on the grounds that it is impossible to estimate accurately the intrinsic activities of individual muscles, as was done by Sherrington (*877*, *910*, p. 285) in his experiments in which he cut cranial nerves III and IV. It is, indeed, difficult to meet either of these objections, but Tilney and Pike are of the opinion that the evidence in favour of synchronous co-contraction in case of the eye muscles is more convincing than that favouring an interpretation on the basis of reciprocal innervation. There remain, however, the beautiful experiments of de Kleyn (*548*, *550*) who has studied behaviour of the eye muscles during nystagmus. de Kleyn has removed the eye-ball in a decerebrate rabbit and connected the internal rectus and the external rectus

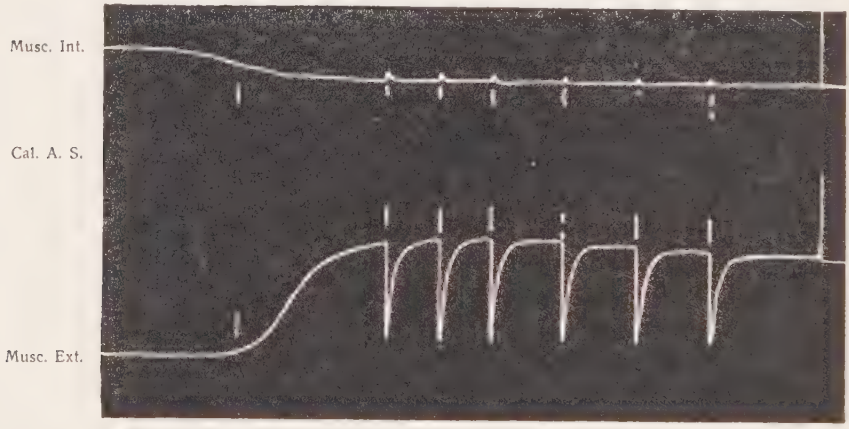

FIG. 183. A record obtained by de Kleyn demonstrating reciprocal innervation of the eye muscles of the rabbit during nystagmus set up by irrigation of the labyrinth. Lower curve, external muscle; upper curve, internal rectus. Movement upward indicates contraction in both curves. Preparation decerebellated. (de Kleyn, *Acta Oto-Laryngologica*, vol. 8, p. 196, 1925.)

muscles directly to accurate recording levers and then caused nystagmus by irrigating one or other of the two labyrinthine organs (running water into the ear). When the ipsilateral labyrinth is irrigated a lateral nystagmus resulted in which the external rectus contracted slowly, and at the same time the internal rectus relaxed correspondingly (fig. 183) until the muscles had reached the full extent of their movement, at which point the internal rectus contracted suddenly and the external rectus relaxed with corresponding rapidity. When, on the other hand, the contralateral labyrinth was irrigated an *internal* nystagmus occurred in which the internal rectus contracted while the external rectus relaxed, and the same series of rhythmic events

(in which the reciprocal features of activity showed itself) was again repeated. It would seem difficult to find a more convincing argument in in favour of the reciprocal activity of a group of muscles than is provided by this simple experiment. It might be urged, however, that the coördination of the eye-ball in such a movement as that involved in nystagmus is due merely to the contraction of one muscle while the other in a Galenical sense remains dormant, being passively stretched by its antagonist. This, however, is clearly ruled out by the fact that when the eye-ball is removed and the muscles are connected to independent levers one muscle could not possibly pull on the other. In other words, the relaxation of the antagonist is spontaneous and synchronous with the contraction of the protagonist. Since this result is so clear-cut after removal of the eye-ball, it is extremely difficult to believe that the result is entirely due to the unnatural condition necessitated by the experimental procedure.

Another point which has been raised by Tilney and Pike as being contrary to the classical view is that in clinical cases in which there is complete paralysis of both the third and fourth nerves on the left side (which produces divergent strabismus to the left) there is no movement of the eye-ball when the patient's gaze is directed toward the right. This is a well-recognized clinical fact and the observation itself cannot be questioned. But that it is contrary to what one would expect on the basis of reciprocal innervation is indeed highly questionable, for in clinical cases of combined oculomotor and trochlear paralysis the pathological condition has existed for a long period and the resulting diminution of activity of the external rectus muscle would long since have caused a disuse atrophy of the muscle. In Sherrington's experiments with monkeys in which nerves III and IV were cut (on the left side) the animals were examined within ten days (*879*). When the animal directed its gaze to the right relaxation of the external rectus occurred and thus permitted a diminution of the divergent strabismus (left). Inhibition of the external rectus (movement of the eye to the right) also occurred in response to cortical stimulation (*879*, *887*). Unfortunately whether or not the power of relaxation of the external rectus diminished with time is not known.

A further point which would be difficult to explain on the basis of the conception of synchronous co-contraction as put forward by Tilney and Pike, is the fact that flexor muscles on being stretched are capable of inhibiting myotatic contraction of their antagonistic extensors. A more apt example of a reciprocal regulatory mechanism than this would be difficult to find. Thus, when the stretch reflex is evoked in an extensor muscle by the application of tension to the patella tendon, the extent

of the resulting contraction would be automatically limited in the intact animal by the tension which the extensor contraction would bring to bear upon the opposing flexor muscles. This plan of reflex organization is clearly of importance in such rhythmic movements as walking or the scratch reflex. Thus, when the flexor phase of the step (involving the lifting of the foot from the ground) is completed, the foot once more touches the ground and the resulting tension brought on the extensor muscles by the weight of the body excites a stretch reflex. This maintains the weight of the body and at the same time pushes it forward, but the extension of the knee-joint which this act involves is automatically cut short by the stretching of the flexor muscles. This, therefore, causes a termination of the extensor phase of the step and initiates the flexor phase.

THE ANATOMICAL BASIS OF RECIPROCAL INNERVATION

In considering the problem of the mechanism of reciprocal innervation it is essential to reduce the reflex arcs involved to the fewest possible constituents. This is of course an arbitrary abstraction, but it assists one in comprehending the fundamental nature of the mechanism. It is clear that the simplest arc must be composed of at least two efferent neurones. Graham Brown (*160*) has introduced the apt term of "half-centres" to describe the site of origin of these neurones; we have accordingly a "flexor half-centre" and an "extensor half-centre." If the extensor muscle is the protagonist, its centre may be referred to as the "primary half-centre." The afferent side of the arc in reciprocal innervation may be looked upon in the simplest case as a single nerve fibre which is capable of influencing the two half-centres more or less synchronously. As Sherrington (*895*, p. 842) has pointed out, this may be brought about in one of two ways: (1) Either the afferent neurone excites the primary half-centres and the primary half-centre in turn inhibits the antagonistic half-centre; or (2) the afferent neurone bifurcates sending out an inhibitory terminal to the antagonistic half-centre and an excitatory terminal to the primary half-centre. This possibility is illustrated in Sherrington's well known diagram (fig. 184).

The evidence in favour of the first possibility is that there exists in the anterior horn cells of spinal motor neurones of mammals von Lenhossek's "side-fibrils," which pass from the axon of the anterior horn cell into the white matter of the cord. Forbes (*318*) and Graham Brown (Jour. Physiol., *48*, p. 18) have suggested that these "side-fibrils" may be concerned in the inhibition of antagonistic muscles. According to this interpretation the anterior horn cell would be primarily activated and would give rise to impulses travelling through the "side-fibrils" of its axon which would cause inhibition

of the antagonistic half-centre. The anatomical basis of this speculation is none too well founded, for it is not known definitely where the "side-fibrils" terminate, and in view of this it is unwise to attach great impor-

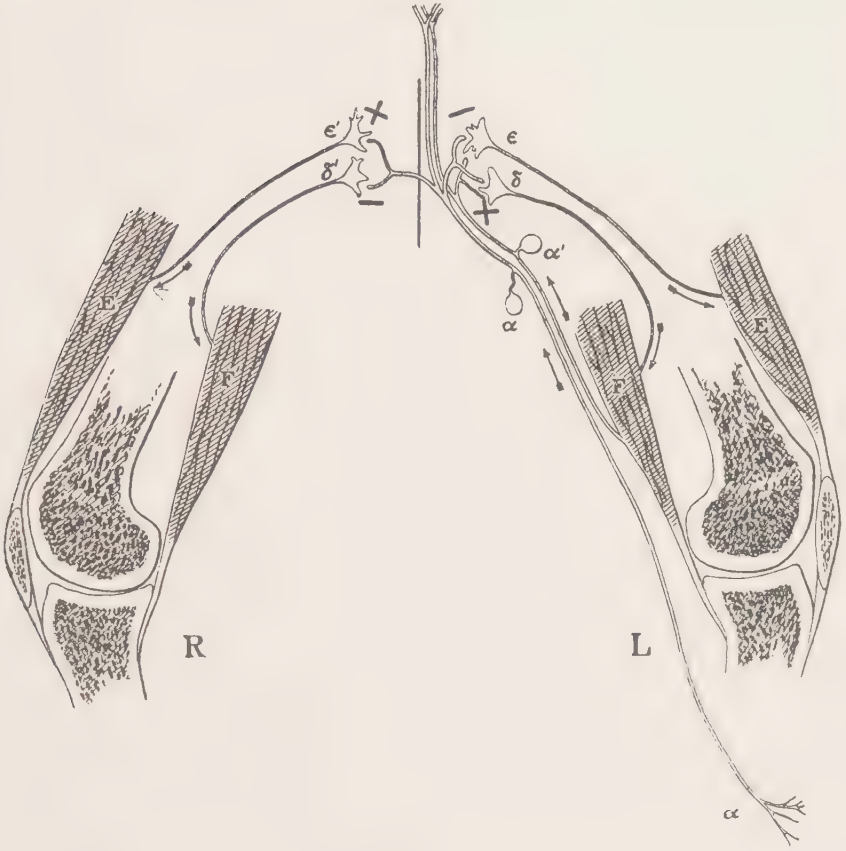

FIG. 184. Diagram indicating connections and actions of two afferent spinal root-cells, a and a', in regard to their reflex influence on the extensor and flexor muscles of the two-knees. a, root-cell afferent from skin below knee; a' root-cell afferent from flexor muscle of knee, *i.e.*, in hamstring nerve; e and e', efferent neurones to the extensor muscles of the knee, left and right; δ and δ', efferent neurones to the flexor muscles; E and E′, extensor muscles; F and F′, flexor muscles. The internuncial neurones which probably exist between the afferent and efferent root-cells are for simplicity omitted. The sign + indicates that at the synapse which it marks the afferent fibre a (and a') excites the motor neurone to discharging activity, whereas the sign − indicates that at the synapse which it marks the afferent fibre a (and a') inhibits the discharging activity of the motor neurones. (Sherrington, *Proc. Roy. Soc.*, vol. 76B, p. 286, 1905.)

tance to it. The second hypothesis has been most generally recognized, having been accepted by Hering (*460*), Sherrington (*910*), Bayliss (*59*), and Fröhlich (*346*). This explanation has a sound anatomical foundation for it is known that many fibres entering through the posterior roots bifurcate within the cord, often many times (Schaffer, *846*). It is not known, however, in what way the inhibitory termination differs morphologically from the excitatory termination, and to this extent the anatomical basis for the theory is unsatisfactory. One argument which has been urged against this explanation is the phenomenon of inhibitory reversal. It is believed that certain poisons, such as strychnine, are capable of converting inhibition into excitation. We shall see, however, that this is an erroneous belief as the apparent reversals are capable of another explanation.

INHIBITORY "REVERSAL" AND STRYCHNINE POISONING

In a normal animal stimulation of an ipsilateral nerve causes reflex inhibition of the extensors. In an animal under the influence of strychnine or in one which has been poisoned in mild degrees by tetanus toxin, stimulation of this nerve may cause reflex excitation of the extensors. This reversal when first observed was believed to be due to a true conversion of inhibition into excitation. Similar reversals in vasomotor reflexes were subsequently described by Bayliss (*59*) in animals subjected to chloroform anaesthesia. But strychnine not only causes this apparent reversal, for it also augments excitatory reflexes. Consequently one might urge that the action of strychnine is not due to true reversal but merely to causing a condition of augmented central excitability in which the excitatory effects produced by stimulation of a mixed afferent nerve conceal the inhibitory effect of the fibres in the same nerve. In keeping with this Magnus and Wolf (*683*) observed (1913) that the tonic inhibitions produced by the neck and labyrinthine reflexes are not reversed by strychnine, and Bremer (*147*) found (1922) that the tonic inhibitory effect resulting from stimulation of the palaeo-cerebellum still exists after relatively strong doses of strychnine. This has recently been amply confirmed by F. R. Miller (*713*) who faradized the "inhibitory area" of the cerebellum before and after *local* application of strychnine. Another opportunity for examination of "pure" inhibitory reflexes after strychnine recently presented itself to Liddell and Sherrington (*640*) as a result of their discovery that traction, if applied to a flexor muscle during a myotatic response of its antagonistic extensor, causes inhibition of the myotatic response. It is evident that the groups of impulses set up by pulling upon a flexor muscle (or by stimulating the tonic

inhibitory tract of the cerebellum) are *homogeneous*, *i.e.*, one has stimulated by an adequate stimulus a group of pure inhibitory end-organs; presumably no fibres producing reflex excitation of quadriceps are excited in this way. Liddell and Sherrington have observed that even with a convulsion dose of strychnine, inhibition still occurs upon pulling a flexor (fig. 185). In other words, a *homogeneous* group of inhibitory impulses is not converted into excitatory impulses by strychnine. The conclusion to be drawn from this is that true reversal of inhibition into excitation probably does not occur and

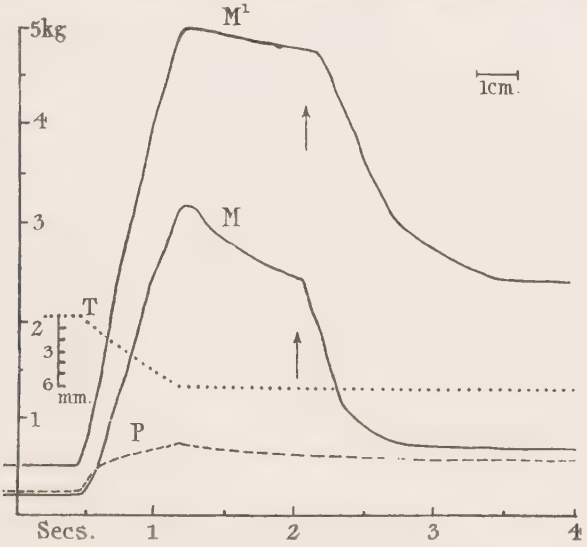

FIG. 185. Responses of quadriceps cruris to table-stretch (T) of 6 mm. before (M and M′) and after (P) severance of its nerve. During each response a stretch of biceps applied commencing approximately at the points marked by the arrows. M the response before, and M′ and P responses after injection of strychnine. (Liddell and Sherrington, *Proc. Roy. Soc.*, vol. 97B, p. 280, 1925.)

the apparent reversal is due to the stimulation of excitatory fibres in a mixed nerve, which, owing to the increase of excitability produced by strychnine, conceals the effect of concomitant inhibition (cf. *745*, *712*, *941*).

THE THEORY OF CHRONAXIE AND STRYCHNINE INTOXICATION

In the first chapter of the present monograph the theory of neuromuscular transmission elucidated by Lapicque has been described, and while very few attempts have been made to apply this illuminating hypothesis to the physiology of the central nervous system, the recent experiments of Bremer

(*152, 153, 154, 155*) and his collaborators have made it evident that the chronaxial conception will undoubtedly throw much light upon the problems of central nervous physiology. According to Lapicque, the power of exciting a tissue rests upon the duration of the exciting stimulus whether this be an induction shock, a condenser discharge, or the action current of a nerve. In the case of nerve and muscle the Lapicque theory postulates that the action current at the motor end-plate is of approximately the same duration as that of the local excitatory process necessary for stimulation of the muscle. For simplicity the "characteristics" of the excitatory process of a given tissue have been measured artificially by condenser discharges and the least duration of stimulus (of double the threshold intensity) necessary for excitation has been termed the "chronaxie.' Lapicque finds that the chronaxie of a motor nerve is approximately that of the muscle which it innervates. This condition is referred to as "isochronism." Now certain drugs have the power of acting preferentially on the time-relations of one or other of the two neuromuscular constituents, *i.e.*, upon the nerve or the muscle. When a nerve-muscle preparation is poisoned, *e.g.*, by strychnine which acts solely on the nerve, it is found that the chronaxie of the nerve diminishes, and when it has diminished to about half its normal value the nerve becomes then unable to excite its muscle. It may so happen that the muscle itself may have been acted upon by drugs which reduces its chronaxie (*e.g.*, nicotine) and a nerve block produced in this way. When strychnine is applied to such a preparation it will restore conductivity owing to the fact that it reduces the chronaxie of the nerve in the same direction as nicotine has reduced it in the muscle.

Bremer and Rylant (*153, 154*) have attacked the problem of the effect of strychnine upon the central nervous system. They find that strychnine has the same action (lowering of chronaxie) on an isolated mammalian nerve as on excised frog nerve, *and they have observed in addition that the chronaxie of mammalian nerve trunks is similarly diminished when strychnine is injected into the general circulation.* Their first experiments were performed upon the lingual-maxillary reflex of Cardot and Laugier. The afferent nerve for elicitation of this reflex is the lingual, and the efferent nerves are two: viz., the anterior nerve to the digastric (the mylohyoid branch of the inferior alveolar) and a branch from the facial nerve. Normally the chronaxie of the lingual nerve was found to be double or treble that of the motor nerves. After an animal has been injected with a minimal convulsion dose of strychnine (0.08 to 0.10 mgm. per kilo) the chronaxie of all the nerves became reduced by 100 to 200 per cent, but the chronaxie of the lingual nerve was reduced more in proportion than the other two, so

that all three nerves came to possess approximately the same chronaxie. Table 15 is taken from one of Bremer and Rylant's protocols. Bremer and Rylant's observation that a convulsion dose of strychnine tends to equalize the respective chronaxies of all nerve trunks involved in a given reflex is one of great importance, and there can be little doubt as to the validity of the inferences which they have drawn from this result. Strychnine breaks down the excitatory barriers between neurones, permitting excitation to spread freely from neurone to neurone throughout the central nervous system (*150*, p. 146). This it does, according to Bremer and Rylant, by equalizing the chronaxie between various contiguous units, which in the

TABLE 15

TIME	NERVE	CHRONAXIE*
		microfarads
4:30–6:15	Lingual [afferent]	0.045
	Anterior nerve to the digastric	0.022
	Inferior facial	0.023
6:14	60 mgm. of strychnine hydrochloride injected into the jugular	
6:15	Lingual	0.014
6:16	Digastric nerve	0.009
6:20	Inferior facial	0.012

* It is common in making chronaxie determinations by means of condenser discharges to express the results in microfarads as in the above tables. For comparison in any given experiment this is quite adequate, but it is not safe to compare results obtained with one set of apparatus with those obtained with another. In the case of frog nerve one may obtain the chronaxie in σ by multiplying the capacity in microfarads by 0.0037 (*350*). This is purely an empirical method worked out by Lapicque, and, while it applies more or less accurately, it is never safe to use it unless the absolute value obtained by it is confirmed by a direct termination with a ballistic or other form of accurate rapid contact breaker designed to give rectangular currents of brief duration. Vogel (1004) with his apparatus found it necessary to use a factor of 0.0052.

normal unpoisoned nervous system are separated by a barrier of heterochronism. Bremer and Rylant (*152*) in a later communication apply this explanation to the problem of antagonistic muscles. They find, for instance, that the chronaxie of the nerve supplying gastrocnemius (internal popliteal) is normally 0.077 mf., while that supplying the flexors of the ankle joint (*i.e.*, the peroneal) is 0.031 mf. After injection of strychnine the latter chronaxie remained approximately the same while that of the nerve to gastrocnemius fell to 0.036 mf. When it had fallen to this extent convulsions ensued in which gastrocnemius and the flexors and extensors of the ankle joint contracted simultaneously. In other words, the mechanism of

reciprocal innervation had been broken down. This does not mean, however, that inhibition as a separate process had been converted into excitation, it merely means that inhibition had been smothered by the extensive spreading of the excitatory process. Inhibition, for instance, is still to be obtained if the superior peduncle of the cerebellum is stimulated or if a flexor muscle is stretched, both of which processes stimulate an apparently homogeneous group of inhibitory nerve endings.

It is a point of great interest that the nerves to the extensor muscles have normally a chronaxie several times greater than the chronaxie of the flexors. This was observed originally by Bourguignon (*137*) and confirmed by Bremer and Rylant. *The chronaxie of an axon is, moreover, an index of the chronaxie of its neurone.* Since the afferent neurones are of briefer chronaxie than extensor neurones they will tend to be separated from the latter owing to heterochronism. Repetitive stimulation (temporal summation) can overcome mild degrees of heterochronism (*600, 554*). Consequently it would seem more than a matter of chance that the recruitment (Chapter XII) should occur in the muscle whose motor nerve is more or less heterochronous with its afferents while recruitment is absent from flexor reflexes whose motor nerves are practically isochronous with their afferents. According to this conception the greater the degree of heterochronism between two contiguous neurones, A and B, the more difficult will it be for neurone A to excite neurone B, *i.e.*, the longer must the stimulus in A be repeated in order to excite B. In keeping with this interpretation Bremer and Rylant have found that in the crossed extension reflex (in which the rhythm of stimulation seldom appears clearly in the responses of the extensor muscles) strychnine appears to break down barriers to such an extent that the rhythm of stimulation appears both electrically and mechanically in the response (cf. also, *304*). Bremer and Rylant find that after strychnine the "primary waves" in the electromyogram in this reflex may become as clear-cut as in a flexor reflex. The nerve to the extensors has, in other words, become isochronous with its afferents and this results in synchronization of impulse formation. After strychnine *recruitment* ceases to be a prominent characteristic of the crossed extensor reflex for it is converted into a *reaction d'emblée.*

We may now consider the origin of the stepping reflex. Though the facts which have been considered give us some information as to how the stepping reflex is regulated, it does not provide complete explanation of how it is initiated in the first instance, or how it is controlled by the higher centres of the nervous system.

THE REFLEX MECHANISM OF STEPPING

The attention of physiologists was first directed to the mechanism of stepping by the early experiments of Goltz (*405*). He found that after removal of the cerebral cortex dogs and cats were still able to walk with full coördination, but their behaviour was characterized by an abnormal restlessness,—not only did they walk but they walked most of the time. Later experiments showed that the whole of the cerebral hemispheres could be removed without impairing an animal's ability to walk about. These observations were repeated and confirmed by a large number of investigators (*e.g.*, *849*) and they proved quite conclusively that the cerebral hemispheres are unnecessary for the maintenance of this reflex. In 1896 Sherrington described (*882*) for the first time decerebrate rigidity and his later investigations showed that the characteristic features of spastic muscles in this condition could adequately be described as exaggerated reflex standing (*909*). A decerebrate animal is thus capable of standing on its feet but locomotion in the ordinary sense of the word is impossible on account of imperfect coördination. However this may be, if a decerebrate animal is lifted from the ground and supported in such a way that its feet hang free, reflex walking, running, or galloping can be very easily elicited, and it often commences spontaneously as soon as the limbs are allowed to hang pendant under their own weight. If quiescent and the pad of one hind foot is pinched, walking may commence, being initiated by a flexor contraction on the side stimulated and an extensor contraction on the opposite side. This is often true whatever the form the stimulus may be, but it is most readily elicited by a painful stimulus. If the stimulus is very intense the animal may actually gallop. There is no doubt but that the rhythmic movement elicited in this way is in every respect comparable to the stepping reflex observed in the intact animal, but owing to removal of the higher centres it is less perfectly coördinated.

What has been said of the decerebrate animal applies also to the so-called *Magnus animal* in which the lower basal ganglia are intact. (In the true decerebrated animal the level of transection of the brain stem passes just caudal to the anterior colliculi.) In the Magnus animal, however, the ease of elicitation of stepping reflexes is much greater than in the decerebrate. If now we consider the *spinal* preparation we find that stepping reflexes are to be elicited in this condition also, but one often encounters considerable difficulty in evoking them, especially in the "acute" condition. The stimulation, for instance, of the pad of the foot must be considerably more intense than is necessary in the case of the decerebrate animal and the type

of stepping which is actually elicited is usually ataxic in character and less perfectly coördinated than in the decerebrate animal. This again is in accordance with the principle of encephalization. For further details see Girndt (*396*).

The nature of the stimulation necessary to evoke a stepping reflex. We have seen that walking may commence spontaneously when the limbs hang pendant ("chronic" spinal dog) and that a painful stimulus applied to the pad of the one hind foot of a quiescent preparation may be sufficient to evoke reflex stepping in the contralateral limb, but there are two other important ways by which this reflex is to be elicited. (1) If in a spinal preparation one stimulates the lateral columns of the spinal cord in the cervical region with a stigmatic electrode, rhythmic stepping reflexes are often set up in the hind limbs (*165*). Often mere mechanical stimulation of the exposed end of the spinal cord sets up walking (*886*, *920*). When the lateral columns are stimulated by a continuous series of break shocks at fifty per sec., the rhythmic stepping may occur at a rate of two or three per sec. In other words, the rate of stimulation has no relation to the rate of response. In this sense, therefore, the stimulus is *continuous*, while the response is rhythmic. Now the lateral columns of the spinal cord contain among other things the pyramidal tracts and we have reason to believe that the pyramidal fibers exert a dual influence on the anterior horn cells which control the hind limb; that is, they contain both excitatory and inhibitory fibres, or at least they contain fibres which terminate (doubly) in excitatory and inhibitory endings. Well known to those who have worked with decerebrate (and spinal) preparations is the reflex "walking" which sometimes commences during an experiment when least desired. It is often found that such walking is due to local irritation of the brain stem at the level of the transection, for one is sometimes successful in stopping it by resecting the brain stem in the same region. (2) The other method which has been found successful in eliciting stepping reflexes in a spinal animal is by stimulating two afferent nerves of opposite reflex effect concurrently. For this purpose the preparation used consists of an isolated pair of symmetrical extensor muscles and stepping is evoked by stimulation of the right and left peroneal nerves (fig. 186). We have seen above in discussing double reciprocal innervation that when two opposing afferent stimuli are nicely balanced there may result perfect algebraical summation in which both antagonists and protagonists contract synchronously. This result, one may add, is sometimes difficult to demonstrate experimentally because unless the balance is perfect (and the stimulation brief) the usual result of opposing inhibitory and excitatory stimuli is

rhythmic contraction similar in every way to reflex walking. In other words, when the spinal centres of the hind limb are subjected synchronously to excitatory and inhibitory stimulation, the extensor ("half") centres on one side first become dominant and then the extensor "half-centres" on the other side and so on. But the excitatory dominance of one or the other is always associated with simultaneous inhibition of the symmetrical "half-centre." The usual effect of opposing stimuli, therefore, is rhythmicity.

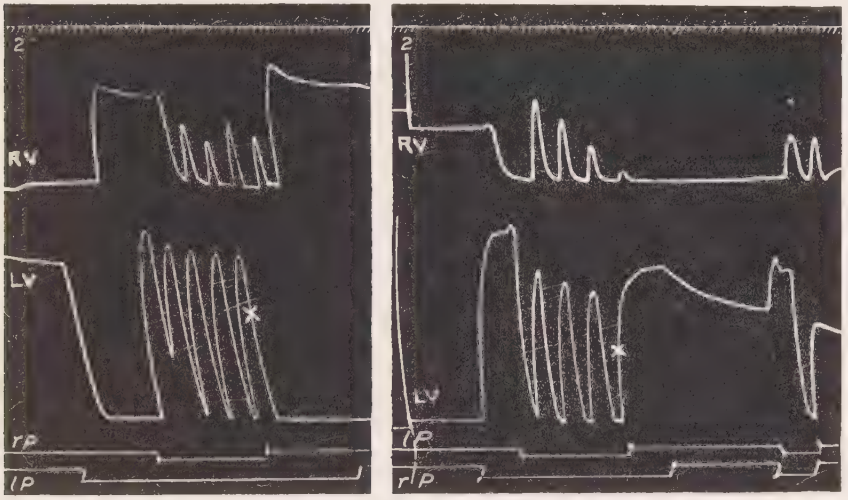

FIG. 186. Symmetrical extensor muscles, RV, vastocrureus, of right knee, LV, of left knee. Rhythmic reciprocal stepping under concurrent stimulation of the antagonistic afferent nerves, *rp*, right peroneal, *lp*, left peroneal. The reflex effect of either of these nerves alone is steady reciprocal excitation and inhibition in the two muscles respectively, as shown in the figure; but so soon as the stimuli are concurrent the reflex becomes rhythmical in both muscles, though still maintaining its reciprocal effect in the two. In figure A the observation begins with faradisation of the left afferent, and that of the right is intercalated; in figure B the arrangement is reversed. The reversed results are shown by the muscles. Decerebrate cat. Time marked above in fifths of seconds. (Sherrington, *Quart. Journ. Exper. Physiol.*, vol. 6, p. 285, 1913.)

In attempting to discover the origin of the rhythmicity the following considerations are important. The fact that the rhythmic stepping occurs in a pair of isolated knee extensors excludes the possibility that the antagonistic muscles and their nerves (severed) are necessary in so far as generation through them of secondary reflexes is concerned. Moreover reflex walking is observed in response to concurrent stimulation of both peroneals after the two isolated extensors have been de-afferented. The

reflex is thus elicitable after removal of all intrinsic afferents as well as the afferents of antagonistic muscles. In fact it is usually more readily evoked after these afferents have been removed than before, as in the case of the simple crossed extensor reflex (Chapter XVII).

The reason why the spinal centres respond rhythmically under these circumstances has been a subject much discussed in the past, and important contributions to our knowledge have been made both by T. Graham Brown (*160*, *161*, *162*) and Sherrington (*920*, *921*). Two possibilities suggest themselves. (1) When a spinal centre has been subjected to excitation it becomes for a short period after the excitation has ceased, more susceptible to inhibition. Or, conversely, if the centre had been inhibited it becomes as a result of this more easily excited. When the inhibition is sufficiently intense mere withdrawal of the stimulus may prove sufficient to cause active contraction (rebound). Stepping may conceivably be due to something in the nature of rebound. But this is unlikely on account of the long latency (Sherrington, *924*) and the fact that walking occurs when all the afferents of the limb have been severed. (2) Another suggestion is that the cause of the rhythmic discharge of the centres is due to the gradual increase of the threshold for excitation or inhibition (*i.e.*, a gradually diminishing threshold for the opposite process) as one or the other of the two processes progresses. "In a reflex centre during inhibition there occurs an intrinsic change, which within limits as it proceeds renders the inhibitory influence less effective and favours the effect upon it of excitatory influence" (*926*, p. 208). This progressive alteration under continuous stimulation is known as "successive spinal induction" (*907*, *910*). With this process in action it is obvious that when excitatory and inhibitory influence converge simultaneously upon the same centre, first one effect will gain dominance and then the other.

From these observations it is not to be concluded that the proprioceptives are without influence upon the stepping reflex. On the contrary, when the proprioceptive nerve supply is intact, the inhibitory effect of stretching the flexors is to be looked upon as an important regulatory mechanism which adds its effect to any intrinsic mechanism existing in the cord. Reflex stepping may be likened to the respiratory reflex in which the afferent vagal impulses, though they regulate the rate of rhythm, *do not necessarily produce it.*

If now we endeavour to account for reflex stepping under the circumstances in which we have observed it, certain cases are relatively simple, but others more difficult. The walking evoked by double peroneal stimulation has been considered. That which results in stimulation of the

lateral columns can be explained on the assumption of the co-existence of excitatory and inhibitory fibres in these tracts,—an assumption well justified experimentally,—and one has grounds of assuming in addition that many fibres have a branched termination (as in the case of nerves supplying the antagonistic muscles of the arthropod claw; v. Uexküll and Grous, *994*), one being inhibitory in effect and the other excitatory (*926*, p. 213). The spontaneous walking occurring when a spinal dog is lifted from the ground probably results from the synchronous interplay of proprioceptive impulses from the muscles of both hind limbs—*i.e.*, something akin to a double stretch reflex. The walking which ensues in strong stimulation of *one* hind limb is more difficult of explanation, but the simple flexor reflex to which it gives rise may in itself lead to concurrent antagonism in the opposed extensor "half-centres" (see discussion of this in *926*, p. 213).

Another important inference which may justifiably be drawn from experiments on the stepping reflex is that in the intact animal the nature of the "influence descending from the higher centres to the spinal centres of the limbs is not an intermittent periodic one whose periods determine the periods of the sequence of the step, and still less does it consist of two alternating period influences,—one determining the recurrence of one phase of the step, the other determining the recurrence of the other phase of the step. The excitation descending to the limb centres is a continuous one whose continuous operation is in a rhythmic manner completely or partially interrupted by an antagonistic reflex reaction secondarily generated in the limb and when the continuously descending excitatory influence is intense it provokes a quicker step than when it is less intense" (*920*, p. 18).

To summarize, the stepping reflex may be elicited from a spinal animal, though for its perfect coördination in the act of locomotion the integrity of the higher centres is necessary. In the spinal condition, however, one finds the basic plan of the reflex and this is characterized by reciprocal innervation of the antagonistic muscles involved. The higher centres exert their control through the simultaneous interplay of excitatory and inhibitory impulses, for it is found that when these two converge simultaneously upon either of the symmetrical extensor "half-centres" of the hind limb, rhythmic stepping results. When under continuous stimulation of this nature, whether it comes from the higher centres of the nervous system or from afferent nerves of the hind limb, first one or the other of the two extensor "half-centres" becomes dominant, the dominance shifting periodically, and reflex walking is the outcome.

SUMMARY

The conception of reciprocal activity of antagonistic muscles, though it originated in antiquity, received its first adequate experimental support in 1893 from the experiments of Sherrington. He found, in the case of the antagonistic muscle group acting at the knee-joint, that traction or massage of the flexors served to inhibit the tendon responses of the antagonistic extensors. Section of the hamstring nerve abolished this effect and caused in addition an augmentation in the knee-jerk. Further analysis led to the discovery of experimental decerebrate rigidity (1896). In the decerebrate condition it was found that stimulation of an ipsilateral nerve caused simultaneous contraction of the flexors and relaxation of the extensors. This observation has been amply confirmed and has become a classical experiment in reflex physiology.

These and other subsequent observations demonstrated conclusively that increase or decrease of contraction does not proceed simultaneously in antagonistic muscle groups. When a flexor contracts, the opposing extensor relaxes owing to reflex inhibition.

Attention is directed to de Kleyn's experiment on the eye muscles. He has found that when nystagmus is produced by irrigation of the labyrinth, the tension of the external and internal recti muscles being recorded by independent levers,—as one muscle contracts the other relaxes correspondingly. Other evidence based on cortical stimulation and on stimulation of the internal capsule is discussed. It is pointed out that the recent criticisms of the conception of reciprocal activity of antagonistic muscles are without foundation, since direct measurements of the tension relations of the muscle groups were not made.

The so-called "reversal" of activity produced by strychnine has been shown to be due, not to a true reversal, but to augmentation of excitatory reflexes to an extent which precludes recognition of inhibitory activity save under special circumstances. It has been found that if, in an animal under strychnine poisoning, a homogeneous group of inhibitors is stimulated, the inhibitory effect invariably shows itself.

The theory of chronaxie has been applied by Bremer to account for strychnine intoxication of the central nervous system. He finds that, whereas normally an afferent nerve has a higher chronaxie than a motor nerve, after strychnine has been administered the chronaxie of the afferent nerve becomes equal, or nearly so, to that of the motor axon. It is suggested that normally excitatory impulses are prevented from spreading in the cord by the slightly different time relation of the reflex constituents. When these

time differences become equalized, as under strychnine poisoning, the normal synaptic barriers existing between contiguous neurones become diminished.

Reflex stepping appears to result from the simultaneous impingement upon a given motor centre of excitatory and inhibitory impulses. Owing to successive spinal induction or to some other as yet ill-understood fluctuation in the excitability of neurones, first one centre is thrown into activity and then the other, the result being the alternate progressive movements characteristic of stepping. It is emphasized that, as in the case of a Hering-Bauer respiratory reflex, an important regulatory mechanism exists peripherally. Thus, in stepping, when the extensor muscles contract, this leads to stretching of the flexors, which in turn causes inhibition of the extensors so that their activity becomes abolished. When the extensor centres "awake" from the flexor inhibition, they become once more thrown into activity, and so the process continues.

CHAPTER XIX

The Significance of the Electromyogram in Voluntary and Other Forms of Reflex Contraction[1]

The previous chapters of the present monograph enable us to approach the complicated problem of interpretation of the electromyogram of voluntary contraction well assured that all phenomena exhibited by contracting muscles are explicable in terms of the all-or-none principle. In order to give a simple elucidation of the problem of the voluntary electromyogram it will be helpful to state at the outset certain *a priori* assumptions made necessary by the adoption of this conception. The justification for these assumptions will appear in the course of the chapter.

When one considers the complex assemblage of the average individual muscle with its multitude of fibres arranged in many directions, and when one reflects upon the tremendously involved connections by which these fibres are controlled in the central nervous system, one realizes the inherent improbability that in any given state of functional activity all the fibres in a given muscle should commence to contract at the same moment of time, or even if they should be provoked into activity synchronously the individual variation in the duration of response of separate fibres would make it impossible for them all to cease activity simultaneously. Experimental evidence of this latter fact has been obtained by careful analysis of single and tetanic contractions of muscles stimulated through their motor nerves. The simplest spinal reflexes, moreover, have been shown to be produced by asynchronous volleys of impulses. As more and more of the brain-stem is allowed to participate in a given response, reflex activities become increasingly asynchronous. The principle of "encephalization" thus applies to temporal dispersion. The higher the level of transection the more delicately graded and sustained is the resulting reflex activity, and there would indeed appear to be some intimate relation between the degree of smoothness of a given contraction and the degree of temporal dispersion involved in its production.

On examining the electrical responses of a muscle in which the individual elements contract asynchronously, one encounters a problem of very great

[1] See Chapter XVI on the electrical responses in the stretch reflex.

complexity, and granting the validity of our presupposition, namely that all activity is due to the summated responses of individual fibre elements,—each response giving rise to an action current,—the following deductions would appear self-evident. The *first is that in a muscle mass in which the single fibre constituents respond serially, the rhythm of the composite electrical response provides absolutely no indication of the rhythm of the individual fibres themselves.* It might be urged, however, that if among a large number of fibres responding asynchronously there were a dominant rhythm, it should be detectable by a Fourrier analysis. Thus, if there were three fibres, each responding at seven per second, it would be possible to deduce from the twenty-one responses to which they would give rise the precise rate of each individual response and the relation in time to the individual

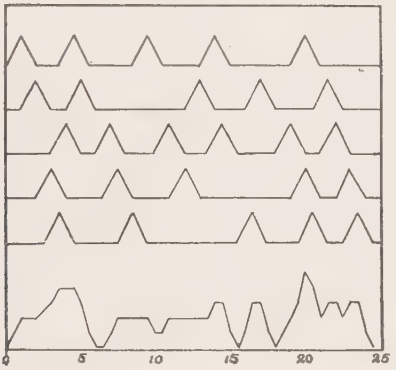

FIG. 187. Hypothetical record of response in muscle of five groups of fibres responding irregularly and out of phase with one another. See text. Time below in σ. (Forbes and Olmsted, *Amer. Journ. Physiol.*, vol. 73, p. 54, 1925.)

responses of the other two fibres (fig. 187). Inasmuch, however, as the muscle with its myriad of units is so much more complicated than this, and inasmuch as each fibre undoubtedly responds at an inconstant rate (*323*), it would be impossible, even if we had an instrument of adequate sensitivity, to deduce anything concerning the individual fibre responses from the composite response of the muscle as a whole. It is owing to the failure to appreciate this relatively simple fact that physiological literature has been burdened and is still being burdened by papers which have attempted to arrive at the frequency of motor nerve discharge from analyses of string records of reflex responses.

Another *a priori* deduction which it is permissible to make is perhaps somewhat less obvious. Recently several investigators have attempted to

determine the rate of discharge of motor neurones by determining the maximum frequency which is to be obtained in the muscle when stimulated reflexly at increasing rates through an afferent nerve. Thus, Cooper and Adrian (*210a*) have found in the flexor reflex of spinal cats that the rhythm of stimulation is to be observed in the electromyogram as high as three hundred per second. This, however, does not prove that *all* the fibres in a given muscle are responding at this rate; it merely indicates that *some* fibres are able to give a response, and it does not prove that these are the same fibres which gave the previous response (*323*). The observed rhythm, therefore, in this type of experiment,—unless we have some definite proof

FIG. 188. Upper line: pneumograph, inspiration upward. Upper galvanometer tracing: leads from the side of the right phrenic nerve. Deflection upward when proximal electrode is negative. Points marked *E*, electrocardiogram.

Lower galvanometer tracing: action currents of the right side of the diaphragm recorded simultaneously with the nerve action currents. Negativity of the proximal electrode produces a deflection upward. Note that the waves in the nerve and muscle apparently correspond. Time in $\frac{1}{5}$ second. (Gasser and Newcomer, *Amer. Journ. Physiol.*, vol. 57, p. 24, 1921.)

that the response is maximal from start to finish,—is unsatisfactory as proof of the maximal rate of response of individual neurone units.

There can be little doubt as to the validity of these two deductions, and I would urge that they are most fundamental to an understanding of the electromyogram of voluntary contraction. There are, however, several possible objections which may be raised with reference to the second deduction. Adrian (*12*) has suggested that under some circumstances all of the central neurones taking part in a given reaction may, so to speak, "beat" together with only a few neurones out of phase with the majority. The beautiful experiment of Gasser and Newcomer (*391*) has been urged as

favouring this assumption. It had long been known that action currents could be obtained from the phrenic nerve during normal respiratory movements (Dittler and Garten, *236*). Gasser and Newcomer, with the aid of a valve amplifier used in association with the string galvanometer, were able to show that during normal respiration each inspiration was accompanied by a series of 100 to 150 action currents recurring at 70 to 100 per second, and simultaneous records taken from the nerve and the muscle showed that each wave in the nerve corresponded with each wave in the muscle (fig. 188). In addition to this they found that if the phrenics on each side were examined simultaneously it was possible to pick out corresponding waves on the two sides. This provided a strong prima facie case for the assumption that the muscle of the diaphragm is innervated by discharges in which each volley of impulses in the nerve produces a corresponding action current in the muscle. This conclusion can scarcely be questioned on any ground. The occurrence of waves makes it evident that a large proportion of impulses are more or less in phase with each other. *But this observation does not prove that each constituent fibre responds at the observed rate.* As we have already emphasized, this conclusion follows *only* when we know that the response is maximal or that the same number of fibres respond continuously throughout. The irregularity in the size of the waves shows clearly that the phase relations of the volleys are not perfect, and in view of observations on the knee-jerk in which *each* electrical response represented a repetitive series of impulses recurring at a high rate, we have no proof that each wave in Gasser and Newcomer's experiment is not similarly a composite of discharges recurring at a high frequency. That each wave in the nerve should correspond with a wave in the muscular response does not exclude such a possibility, and this is equally true of the interesting experiments of Bass and Trendelenberg (*56*). Apart from Gasser and Newcomer's evidence, which is admittedly suggestive, there is little adequate ground for believing that neurones in a given centre ever do "beat" exactly in phase. Consequently, in the absence of such proof it may be justifiably concluded that summated electrical responses, either of whole nerves or of muscles during reflex activity, nave not, and probably never will provide an adequate basis for determination of the rate of discharge of single constituents.

Not until the responses of individual units can be recorded singly will electrical records give a decisive answer as to rate of discharge of spinal motor neurones. Already, however, Adrian and Zotterman (*13a*, *19*) have succeeded in recording the action currents of a single proprioceptive afferent nerve fibre responding to an adequate stimulus (stretch) applied to its end-organ. In addition to the importance of so great a technical achievement,

it also promises that a definitive solution of the long-debated question of the intrinsic rhythm of spinal centres may be reached in the near future.

With these points in mind, we may proceed to a brief historical account of the investigations of the voluntary electromyogram.

THE INTERPRETATION OF THE VOLUNTARY ELECTROMYOGRAM

In order to appreciate the early beliefs concerning the voluntary electromyogram it is essential to have an adequate realization of the point of view which existed before the all-or-none principle of fibre response had become firmly established. To a generation which has been brought up on the all-or-none theory, the early stages of the controversy might seem difficult to understand. It was less than twenty years ago, however, when physiologists believed that nerve impulses vary in size and that increasing degrees of voluntary effort were bought about by increasing the size of our nerve impulses. And it was scarcely thirty years ago that nervous influence was looked upon as continuous in nature rather than as a series of discontinuous impulses. Now, thanks to the brilliant investigations of Lucas, Adrian, Pratt and others, many physiologists feel completely confident that all variations and gradations in muscular responses are explicable in terms of variations, on the one hand of the *rate* and *duration* of discharge, and on the other of the *number* of discharging units. Or, as we have referred to it in the present monograph, all variations in muscular activity are explicable in terms of "multifibre" and "wave" summation.

Burdon Sanderson (*180*, *181*) was one of the first to investigate the electrical reactions of muscles when in a state of prolonged contraction. He examined among other things the electrical responses of muscles in strychnine spasm. The majority of these investigations were carried out by his pupil, Florence Buchanan (*174*), who after Burdon Sanderson's death continued her researches, which culminated in a series of important contributions on the rhythm of the electromyogram (*175*, *176*, *177*, *178*). Shortly after Buchanan had commenced her investigations, Piper (*774*) in Germany attacked the same problem, confining his attention more particularly to the electrical responses in voluntary contraction.

Buchanan observed that in strychnine spasm of the decerebrate frog, when recorded with a capillary electrometer, there appeared large undulations in the record at frequencies of three to fourteen per second and upon these were superimposed smaller undulations having frequencies between 40 and 100 per second. To the larger undulations she gave the name of "waves" and to the smaller "wavelets." The question arose from these experiments as to which, if any, of the undulations were due to muscle

rhythm and which were due to nerve. It was possible that the muscle might give rise to one rhythm and the nerve to the other. To test this question she separated the gastrocnemius muscle of a decerebrate preparation in such a way as to leave it connected with the remainder of the preparation only by its nerve. The muscle was then placed in a moist chamber the temperature of which could be varied, and in this way the temperature of the muscle was altered without altering the temperature of the remainder of the preparation. She found that by this procedure she could raise and lower the frequency of the wavelets without altering that of the waves: thus at 7° the wavelet frequency varied from 40 to 54 per second and at 16°

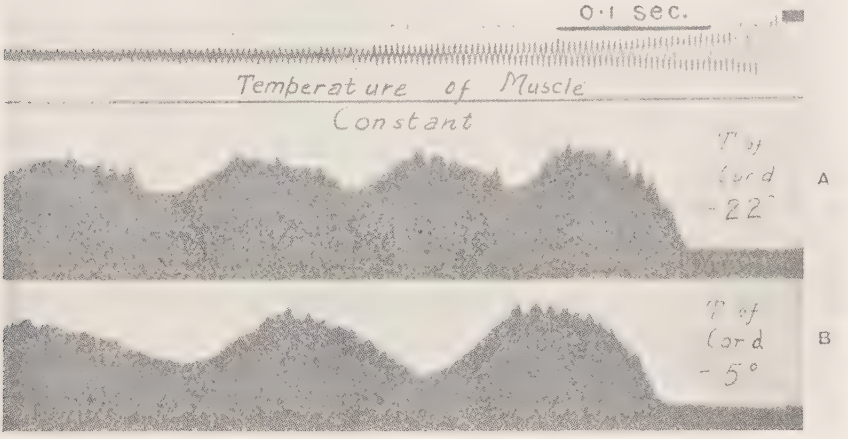

FIG. 189. Reflex electrical responses of frog's triceps femoris (strychnine). Muscle at 12°C. in both. Water running through glass tube over spinal cord at 22° in A, at 5° in B. Recording surface moving horizontally, rate indicated by 100 fork tracing above the signal *s*. (Buchanan, *Quart. Journ. Exper. Physiol.*, vol. 1, p. 217, 1908.)

it lay between 100 and 110. From this it was inferred that the wavelets do not correspond to any central nervous rhythm but are the result of an intrinsic rhythm of the muscle itself. To confirm this conclusion she altered the temperature of the spinal cord while keeping the temperature of the muscle constant, and by so doing she found that the frequency of the waves changed but not of the wavelets (fig. 189). From this she drew the inference that the waves are associated with central nervous phenomena. Her results have recently been confirmed by Cooper and Adrian (*210*) in a series of experiments in which the temperature of the spinal cord was more carefully controlled, and the conclusions were shown also to apply to the muscles of a spinal cat. They found that the "after-discharge" (wavelets)

diminished when the cord was cooled locally. Cooper and Adrian (*210a*) however, concluded in the case of the cat that the limiting frequency of central discharge is 240 to 320, while the muscle (tibialis) stimulated through its motor nerve responds up to 400 per second. According to their interpretations the central neurones do not discharge more rapidly than the muscle fibres can respond.

Buchanan suggested that the waves and wavelets corresponded to the well known appearance of the human electromyogram as investigated by Piper (*774*). As is well known, Piper found that the electromyogram of a muscle when executing a voluntary movement displays a series of large waves recurring at approximately 50 per second, and between these waves a series of smaller oscillations which Buchanan believed to correspond with her wavelets. She concluded, accordingly, that the secondary oscillations in the electromyogram were the result of the intrinsic muscular rhythm while the large waves were of nervous origin. Piper, however, has placed another interpretation on his own results, *i.e.*, that the rhythm which appeared in the myogram was clearly the result of a nervous rhythm and in fact the rate of discharge of the central motor neurone could be inferred from the electromyogram. This conclusion has been the subject of much controversy, and many authors (*176*, *424*, *384;* see Adrian, *12*) have been unable to repeat Piper's experimental results, finding that the voluntary electromyogram might show rhythm varying from 5 to 500 per second and only a few authors have been able to obtain the dominant rhythm of 50 per second reported by Piper. Forbes and Cattell (319) point out that rhythms of indefinitely high frequency may be observed provided only one's galvanometer string is of sufficiently small mass (see below fig. 192). Buchanan performed the interesting experiment of stimulating the median nerve of the human forearm at Piper's rhythm of 50 per second, and she observed that the resulting contraction of the flexor muscles of the wrist was relatively ineffectual. She suggested in view of this that the central nervous rhythm was undoubtedly higher than 50 per second.

Forbes and Rappleye (*324*) have examined the effect of temperature upon the electromyogram of human finger and arm muscles during voluntary contraction. They immersed the member in water of 4° to 6° until ample time had elapsed for local cooling, and then the electromyogram was recorded; similarly records were taken at normal body temperature, and after the arm had been immersed in water of 46° to 47° (fig. 190). Under these circumstances the body temperature remained constant (mouth). They found that the rhythm exhibited in the forearm flexors at normal temperature may be ± 100 per second and might increase to 130 to 140

when in hot water; when the arm had been cooled in water of 4° the oscillations of the electromyogram became larger and less frequent (35 to 45 per second). They, accordingly, agree with Buchanan that the actual rhythm observed in the electromyogram probably owes its origin to peripheral conditions. They also find, in agreement with Piper, that the rhythm of

FIG. 190. Electromyograms of first dorsal interosseous muscle; adduction of forefinger against table. A, after fifteen minutes' immersion at 7°C. B, after four minutes' preliminary immersion at 40°C. C, after final immersion, fifteen minutes at 47°C. In all figures the upper line recording movements of the string, shows by upward excursions negativity in the electrode placed over the belly of the muscle. The lower line records time; each complete vibration = 0.01 second. (Forbes and Rappleye, *Amer. Journ. Physiol.*, vol. 42, p. 236, 1917.)

stimulation is *independent* of the strength of voluntary contraction. Adrian (*12*) has pointed out that the cooling of the proprioceptive endings in Forbes and Rappleye's experiment may account for the apparent diminution of frequency since Dusser de Barenne and Brevée (*259*) have found that a similar phenomenon occurs when proprioceptive activity is abolished by

injection of novocaine into the muscle. This cannot, however, explain away the whole matter for cutting of the posterior roots in Fulton and Liddell's (*364*) experiments actually increased the observed rhythm of the crossed extensor reflex (Chapter XII). However, it is possible that temperature alterations and novocaine affect one functional group of proprioceptor endings more than another.

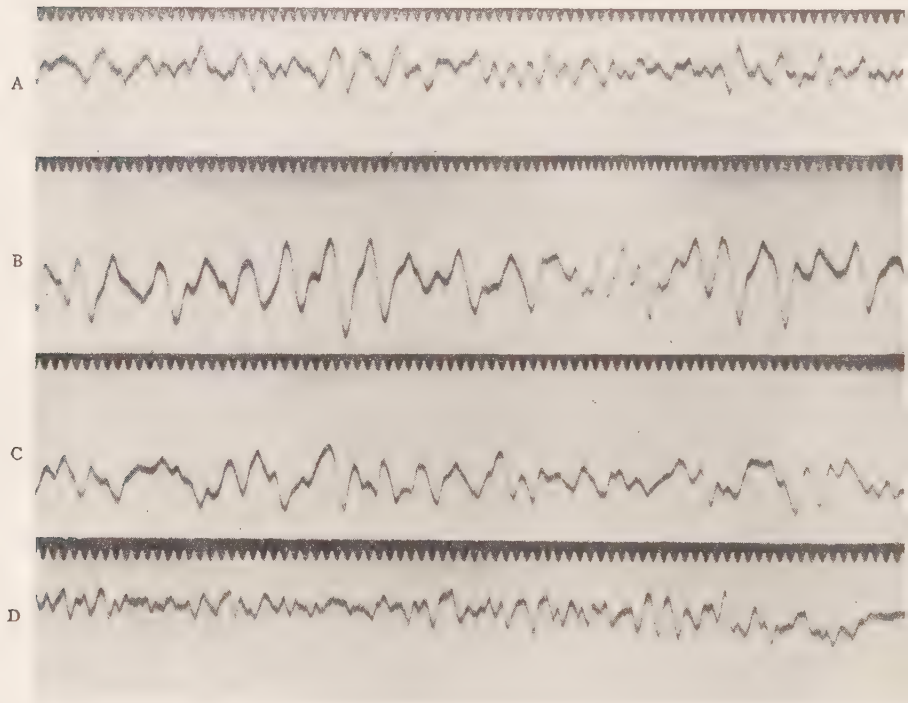

FIG. 191. Records showing the behaviour of action currents during fatigue of voluntary contraction. The tuning fork marks hundredths seconds. The subject lifts "as hard as he can" against an immovable object; the electromyograms are taken from the flexor muscle.

A. *At the onset of the contraction.* The frequency of chief oscillations is 58 per second, their average amplitude being 4.4 mm.

B. *After the steady muscular contraction has been continued for 30 seconds.* Frequency 40 and amplitude 6.5 mm. The subject complains of slight fatigue.

C. *At 60 seconds,* the subject complaining of painful fatigue. Frequency of action currents is now 32 per second and average amplitude of the waves 9.5 mm.

D. *After a rest of 60 seconds* this record is taken near the onset of a new contraction, all the adjustments being just as in C at the end of the fatigue period. The frequency of action currents has returned to normal, 52 per second, and the amplitude of the main wave has fallen to 5.0 mm. (Cobb and Forbes, *Amer. Journ. Physiol.*, vol. 65, p. 245, 1923.)

Cobb and Forbes (*204*) have made the interesting observation that the rhythm of the voluntary electromyogram of human beings diminishes in frequency but the oscillations increase in size as the muscle becomes fatigued. In figure 191 is reproduced a record taken before and at the end of a severe exercise which led to almost complete exhaustion of the muscle. The observations of Cobb and Forbes are significant as they appear to throw important light upon the nature of voluntary contraction. Consequently their results demand careful consideration. They suggested that the diminished frequency with increased size of the action currents in fatigue might be explained by appeal to the facts already known concerning neuromuscular conduction. They point out that if a block occurred at the end-plate owing to fatigue, the resulting diminution in frequency of the nerve impulses (reaching the muscle) would be sufficient to account for the observed diminution in frequency in the string records. The fact that subnormal impulses would in this way be blocked out would have the secondary effect of increasing the total size of those which actually passed. This ingenious explanation rests upon two important assumptions both of which demand further examination. (1) They assume that inasmuch as nerve trunks are unfatiguable the results of their experiments cannot be explained on the grounds of alteration in the nerve impulse frequency owing to fatigue. That the axones of nerve fibres are, in fact, unfatiguable, or or practically so, cannot be questioned, but, as Piper (*773*) has pointed out, voluntary contraction involves *the setting up of impulses* in the cortex of the brain, and there is ample evidence for believing that the process by which nerve impulses are controlled at the higher levels of integration is one eminently susceptible of fatigue. This was early pointed out by Waller (1891, *1015*) in his interesting paper on the "Sense of Effort." He observed that voluntary effort cannot be pushed to such an extent that a block occurs at the motor junction because central fatigue supervenes. Added to this is the well known fact that the power of voluntary effort is greatly diminished in conditions of severe mental fatigue. This clearly suggests that the possibility of central fatigue must be taken into consideration in accounting for Cobb and Forbes' observation (cf. *24*).

(2) Their second assumption is that in voluntary effort nerve impulses follow each other at such a rate that succeeding impulses may be of subnormal magnitude. The evidence for this assumption has been carefully considered in a recent paper by Forbes and Olmsted (*323*). They point out the weakness of Adrian and Cooper's evidence which led them to the conclusion that the upper limit of the rate of discharge of impulses in the spinal cord of a cat was 300 per second. They emphasize quite rightly

that when the string galvanometer records are considered statistically and due allowance is made for the fact that the impulses occur asynchronously it is quite impossible to determine from the rhythm of the string the rate of discharge of individual neurones (fig. 192). In this conclusion we would entirely concur.

The assumption that impulses follow so rapidly as to fall in the refractory phase, demands that the rate of discharge shall be 500 to 600 per second. As positive evidence that such rates do occur, Forbes and Olmsted describe experiments in which alcohol applied to a limited region of the popliteal nerve served to block reflex responses before the responses of the motor nerve (fig. 193). They have inferred from this that in reflex responses some impulses are of subnormal magnitude and consequently are more vulnerable to a region of impaired conductivity than are full-sized impulses set up by motor nerve stimulation. The conclusion is important and the evidence on which it is based appears to be adequate. They have discussed very completely the possible objections which may be raised against the conclusion.

One possible objection we may examine further. Maximal responses probably never occur in reflexes. Consequently, there are fewer fibres involved in any given reflex response than in a maximal motor response. Since an alcohol block does not affect all fibres to the same extent, there is a greater statistical probability that the fibres responding to reflex stimulation could be blocked before abolition of responses elicited by maximal stimulation. However, since the time intervals between extinction of reflex activity and that of motor nerve responses was in many of Forbes and Olmsted's experiments considerable, it is unlikely that this is an insurmountable objection.

In experiments on inhibition of the knee-jerk (discussed in Chapter XIII) direct evidence was provided that the average rate of discharge during a 30σ interval was not greater than 250 to 300 per second. In the spinal condition the anterior horn cells are completely released from the normal inhibitory control exerted by the higher centres and are therefore in a maximum condition of excitability. Under such circumstances a single

FIG. 192. Electromyograms of decerebrate rigidity and crossed extension reflex showing variations in size and frequency of action currents when recording with different strings. (1) Records in absence of stimulation; (2) at beginning of reflex response; (3) at height of contraction. In each experiment leads were on gastrocnemius muscle, and the Hindle galvanometer with gilded quartz string was used.

A. 17,000-ohm string, 2.75μ diameter, tension 174 m. per ampere. Magnification 490.

B. 4,800-ohm string, 2μ diameter, tension 60 m. per ampere. Magnification 490.

C. 19,500-ohm string, 1.5μ diameter, tension 41 m. per ampere. Magnification 490.

D. 16,800-ohm string, 1.25μ diameter, tension 170 m. per ampere. Magnification 858. (Forbes and Cattell, *Amer. Journ. Physiol.*, vol. 70, p. 159, 1924.)

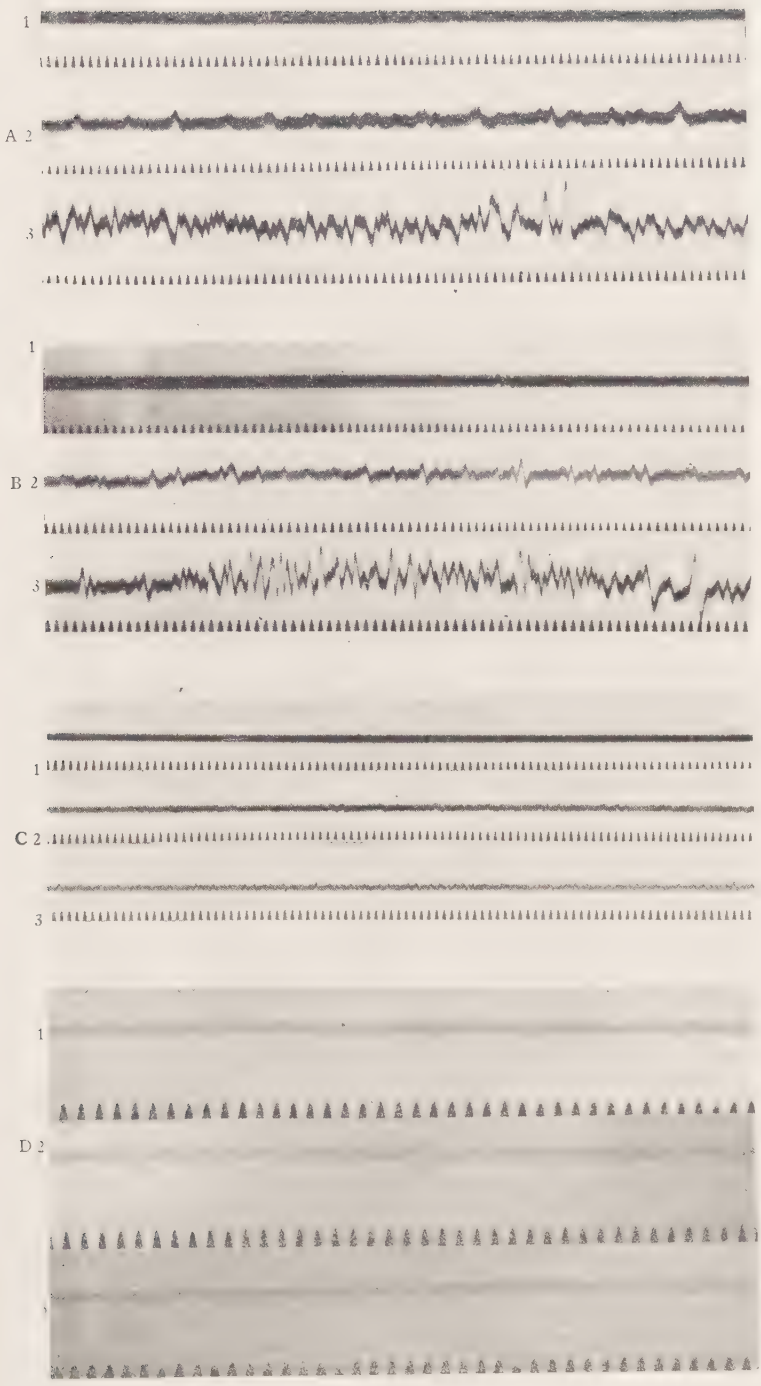

FIG. 192

afferent volley of impulses gives rise to a short tetanus. It is evident that somewhere in the reflex arc elements are subjected to a form of stimulation which is supramaximal in the sense that it sets up several volleys of impulses. As there is no restraint (*e.g.*, no inhibitory control) in the spinal condition, it is reasonable to believe that when thus stimulated the anterior horn cells

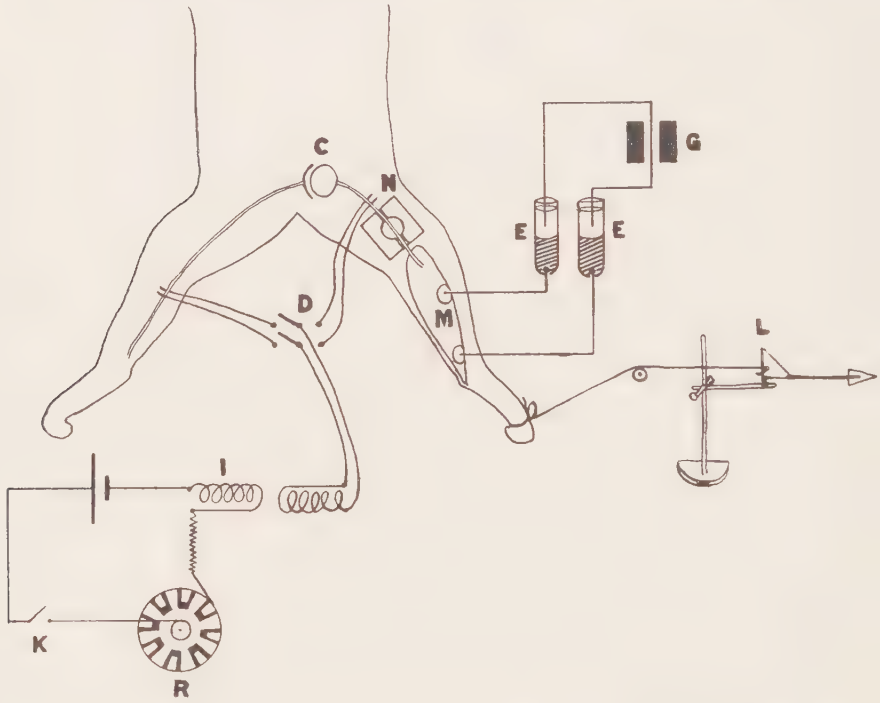

FIG. 193. Diagram to show arrangement of preparation and apparatus for determination of the rate of discharge by the alcohol block method. I, inductorium. K, key in primary circuit for single shocks. R, rotary interrupter for tetanizing stimuli. D, double-pole double-throw switch to shift stimulation from afferent to motor nerve. C, spinal center. N, narcotizing cup on motor nerve. M, gastrocnemius muscle, E, E, agar electrodes. G, string galvanometer. L, muscle lever for recording on kymograph. (Forbes and Olmsted, *Amer. Journ. Physiol.*, vol. 73, p. 23, 1925.)

would respond at their maximum rate of frequency, and from Forbes and Olmsted's evidence it would appear that this might possibly be, for the first few volleys, higher than 250 per second. If, however, one visualizes the central excitatory process as one in which there occurs at the axon hillock of the nerve cell a concentration of ions, which so long as it is above a

certain value continues to give rise to motor nerve impulses (Chapter XIV), it is somewhat difficult to believe that such a mechanism would be capable of setting up responses in the relative refractory period, just as it is difficult for a motor nerve to set up an impulse in a muscle fibre during the relative refractory period. But as this is a question which depends largely on one's view concerning the nature of the central excitatory process, and as adequate experimental evidence from analysis of the rate of discharge of single fibre units is not yet available, one cannot profitably pursue the question further.

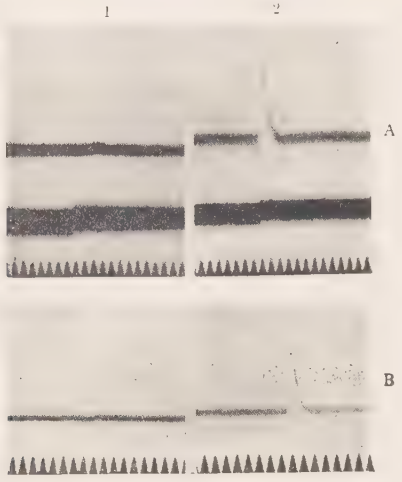

FIG. 194. String galvanometer records showing (1) monophasic response of extensor motor nerve to single maximal induction shocks applied to the afferent nerve of the opposite side and for comparison (2) records of monophasic response of the same motor nerve to direct maximal stimulation. Time = 0.01 second. (Forbes and Cattell, *Amer. Journ. Physiol.*, vol. 70, p. 144, 1924.)

How then are we to account for Cobb and Forbes' observations? The suggestion that the augmented action currents in fatigue are due *entirely* to blocking at the motor junction, is unlikely, yet it is highly probable that such a block in a mild form does actually occur, and that therefore this is a factor to be considered in interpreting their result. The accumulation within the muscle fibres of acid metabolites increases the threshold of excitability and *diminishes the size of the action current* (Chapter VIII). But a diminution in size of individual action currents, which undoubtedly occurs when a muscle is fatigued, would have precisely the opposite influence upon the size of the action currents from that observed in Cobb and Forbes'

experiments. The only other possible way in which the action current of a voluntary contraction could become increased in size is by the occurrence of greater synchronization among the individual volleys. The question at issue, therefore, is the mechanism of synchronization in fatigue.

An observation bearing upon this question is that familiar to everyone, that after carrying a heavy weight until the arm is painfully fatigued there occurs a fine tremor which may persist for an hour or more after the weight has been put aside ("fatigue tremor"). This was observed in 1751 by Robert Whytt (*1042*) and clearly described. Such a tremor partakes the characteristics of a rapid clonus. The rate of the clonus varies from 13 to 30 per second, which is within the limits observed by Viets, Cobb, and others for a pure clonus resulting from an upper motor neurone lesion. The rate of response in Cobb and Forbes' records of fatigued muscle is approximately 20 per second which suggests that the two phenomena have a common cause. That the clonus is similar to that occurring in an upper motor neurone lesion suggests that fatigue of the upper motor neurones is in fact the cause. If this were the case, the cause of the synchronization would be the same as that of the clonic responses of the decerebrate animal (Chapter XVI), *viz.*, synchronous stimulation of afferent endings which tends to occur whenever there is slight tension (as with the arm hanging pendant under its own weight) applied to a somewhat spastic muscle.

Another possibility to be considered in Cobb and Forbes' experiments is in an alteration in the proprioceptive control of the muscle. It might conceivably be that the acid metabolites affect the threshold of excitability in the proprioceptive nerve endings. It is known that these endings are notoriously sensitive to alterations in the circulation. There is so little first-hand information, however, concerning the effect of fatigue on the proprioceptive endings that it would be unsafe to place much emphasis upon such a factor.

In this connection one may recall the interesting experiments of Hoffmann (*491, 492, 493*) and of Preisendörfer (*785*). They have studied the relation of the tendon jerk to voluntary contraction and have observed this interesting phenomenon, namely, that if tendon reflexes are elicited at a high rate (*e.g.*, 50 per second), there occurs a pronounced augmentation in the amplitude of successive electromyograms if voluntary effort is superadded to the tendon responses. They suggest that under these circumstances, *voluntary contraction appears to be little more than a series of augmented tendon reflexes;* the rate of the myotatic responses have, as it were, determined the rhythm of the spinal arcs, and the effect of cerebral activity has been to lower the "synaptic resistance" of these arcs, with the result that more ample myotatic reflexes ensue. Hoffmann specifically suggests that the tendon reflexes may possibly be an elementary form of reaction out of

which the whole complex of postural reactions of the musculature are developed, but some critics (*e.g.*, F. M. R. Walshe, *1020*) are skeptical of his conclusion. In view of what is now known regarding the stretch reflex, it is evident that Hoffmann's suggestion is of the utmost importance. Moreover, his observations on the influence of the cerebrum have led to the suggestion that voluntary activity is little more than a "release" phenomenon; that is, myotatic reflexes are constantly being set up, especially in antigravity muscles, and voluntary activity is conditioned by the degree of cerebral inhibition, which determines how great shall be the response to any given myotatic stimulus. We shall refer to this again in the following chapter.

Let us return once more to the problem of the significance of the rhythm observed in the voluntary electromyogram. When, as in the case of a fatigued muscle or a cooled muscle, a rhythm is prominent, it is evident that successive volleys of impulses are arriving more or less in phase, but that each wave in the electromyogram represents a single volley of impulses is highly improbable. One need only cite the case of the spinal knee-jerk in which a tetanus of four or more volleys gives rise to an apparently single electrical response. Hoffmann's view would indeed appear to be nearer the truth; *i.e.*, that when well marked rhythms are observed, the muscle is really in a state of imperfect clonus in which each contraction of the clonic response is made up of several closely timed volleys of impulses,—a series of rapidly recurring "knee-jerks." Adequate higher control destroys the discontinuities in the response so that the contraction becomes more or less smooth. In fact the essence of coördination is smoothness of response. Higher control is apparently achieved by causing the responses of the individual units to become completely out of phase.

We have found reasons for believing that the excitatory impulses responsible for postural responses and stepping reflexes come largely from the so-called stretch afferents within the muscle. Whether or not these excitatory impulses become effective depends upon the extent of release from inhibition of the higher centres. If we adopt Hoffmann's conception, voluntary contraction may in fact consist almost entirely in release of the lower motor neurones from higher inhibitory control. It may be emphasized, however, that the motor cortex is also capable of exciting the anterior horn cells *de novo*, but in view of the tremendous tension which a muscle can develop when its stretch afferents are stimulated it seems highly probable that voluntary *excitatory* impulses are relatively unimportant as compared with excitatory impulses arising in the muscle itself. It seems justifiable to urge, moreover, that when for any reason there is undue

"voluntary" fatigue the resulting clonus ("fatigue tremor") is in reality caused by partial removal of the higher influence.

SUMMARY

Owing to inevitable temporal dispersion of fibre activity in such highly integrated reflexes as are concerned in voluntary contraction, it is unjustifiable under any circumstances to infer from the observed (summated) action current rhythm of a voluntarily activated muscle, the rate of response of the individual fibre units. Even in the case of so simple a reflex as the spinal knee-jerk, the recorded electrical variation does *not* reveal the fact that the reaction is a short tetanus involving all participating fibres. The galvanometer string, when recording a reflex muscular response, may be likened to a Brownian particle bombarded on all sides by minute forces, upon which only occasionally do the (action current) forces impinge sufficiently in unison to produce a recordable deflection. Consequently, as Forbes and Cattell have emphasized, the observed rhythm of a reflex (*e.g.*, the extensor reflex) if a function of the mass of the galvanometer string rather than of the physiological activity of the muscle. When artificial rhythms are imposed upon the organism from outside, provided after-discharge is not too extensive, action currents do recur at intervals determined by the rate of stimulation. Normal voluntary activity, however, is not the product of an artificial external rate of stimulation but of a myriad of afferent rhythms integrated from the sensual data supplied by every receptor organ in the body.

When well-defined rhythms *are* observed in normal voluntary activity (or under pathological conditions), it indicates that a group of fibre units responded sufficiently in unison to give the response, but we have no proof, from one action current deflection to the next, that the same group of fibres is in activity, and in the absence of such proof we again cannot infer the rate of unit discharge. Recent experiments of Forbes and Olmsted have given suggestive evidence favouring the assumption that the rate of discharge of a given neurone of the final common path is inconstant, and it is pointed out that this conclusion appears to be a necessary consequence of Sherrington's conception of the central excitatory process.

Hoffmann's view that voluntary contraction is produced by releasing myotatic reflexes from inhibitory control is looked upon as an important contribution to theory of cortical control.

CHAPTER XX

The Cerebellum

Extensive morphological, clinical and experimental investigations have as yet failed to provide adequate knowledge of the functions of the cerebellum, though important contributions have been made by distinguished neurologists of many nations, notably von Haller, Rolando, Flourens, Magendie, Wier Mitchell, Ferrier, Nothnagel, Luciani, Sherrington, Horsley, Babinski, Langelaan, Bárány, van Rynberk, Dusser de Barenne, Rossi, Ingvar, Bremer, Magnus, Rademaker, and many others.[1] In entering upon a discussion of the cerebellum attention must first be directed to the admirable general accounts already available. Most important are those of Sherrington (*896*) who in 1900 published an invaluable critical description of the material then at hand; Luciani (*666*) whose epoch-making experiments, though first published in 1891, were extended, and subsequently were made available for English readers in 1915 by the translation of his Human Physiology (*667*, vol. 3, p. 419, *et seq.*); van Rynberk (*834*, *835*) who has recently summarized with great thoroughness and care the evidence concerning cerebellar localization; Holmes (*496*, *497*) whose valuable clinical experience during the war was published in 1922; Tilney and Riley (*987*, *989*) who have given an extensive account of the structure and connections of the cerebellum; Herrick (*465*) who has investigated exhaustively its phylogenetic development; and finally Miller (*711*) who has provided a useful review of the 'physiology' of the cerebellum. The material given in this chapter is based largely upon these sources, but due account is also taken of the recent important experiments of Bremer (*147*, *151*), Ingvar (*511*), Dusser de Barenne (*256*), Rossi (*823*, *824*, *825*), Magnus and Rademaker (*679*, *788*).

For purposes of exposition the views concerning the function of the cerebellum may be divided into two groups. One school of investigators, led especially by Bolk, André-Thomas, van Rynberk and Bárány, have

[1] The historical aspects of experimentation on the cerebellum are to be found in J. Soury's exhaustive history of the doctrines relating to the central nervous system (*960*). A useful historical account of the cerebellum is also given by Sherrington (*896*). An extensive bibliography of recent literature is to be found in van Rynberk's monograph (*835*).

maintained that discrete morphological units of the cerebellum govern specific muscle groups, much as certain portions of the motor area of the cerebrum *appear* to control restricted parts of the body musculature. Another group of investigators, led by Luciani, Sherrington and others, have insisted that the cerebellum is to be looked upon as a single functional unit, the only well-defined anatomical division of function being in respect of the two halves of the organ, each one presiding over the body musculature of its own side.

This latter view is set forth in the following quotation (*896*, p. 908): "The muscular mechanisms of progression and pose, the innervation of which may, as above suggested, be centred together, *perhaps in the thalamencephalon*, are of wider spatial distribution, and employ not one side of the trunk but both sides, not one limb but all four. Often they probably involve the musculature of the entire body. It is because of its intimacy of connection with such movements as these that the cerebellum is an organ which justifies Hesiod's ὅσω πλέον ἡμισυ παντός. The division into hemispheres and middle lobe is founded merely upon gross anatomy. The organ commonly, probably always, 'functions' as a whole. Luciani is right to insist on this, and the reason that it 'functions' as a whole seems clearly because it is so largely a piece of mechanism that deals with the innervation, not of this or that piece of musculature, but of the musculature of the body as a whole."

In addition to these somewhat opposed views, several writers (Rossi, *824;* Miller, *711*) have taken a middle ground admitting that there may be a "prevalence of representation" of muscle territories in certain large anatomical divisions of the cerebellar lobes.

To examine critically the evidence for and against these interpretations must be one of our problems in this chapter. Before entering upon such a discussion, however, it is desirable to mention the recent remarkable discoveries of Magnus and Rademaker relating to the cerebellum. They are of especial value to us at this point, not for their positive evidence, but for the fact that they define in no uncertain terms what the cerebellum does *not* do. Magnus and his collaborators have described the various attitudes of the body which are assumed in response to altered needs of the animal, namely, the "tonic neck reflexes," the "tonic labyrinthine reflexes" (utricle and saccule), and the five "righting reflexes." These reflexes as is well known, cause alterations in the distribution of the postural tone of the body musculature. As Miller (*711*) has remarked, they are precisely the type of response which one would expect to depend upon cerebellar paths, yet Magnus and his co-workers have shown that all three groups of postural reflex ("labyrinthine," "neck," and "righting") persist unmistakably after removal of the cerebellum, in fact they are usually more readily elicited after the operation than before. Decerebellated cats, dogs and rabbits have

been kept alive for periods up to two years following the operation always with the same result. In Magnus's words (*680*, p. 352):

"Experiments have proved that all postural reflexes are present and perfectly undisturbed after total extirpation of the cerebellum. Therefore their centres as well as their afferent and efferent tracts are extracerebellar. Through the brilliant investigations

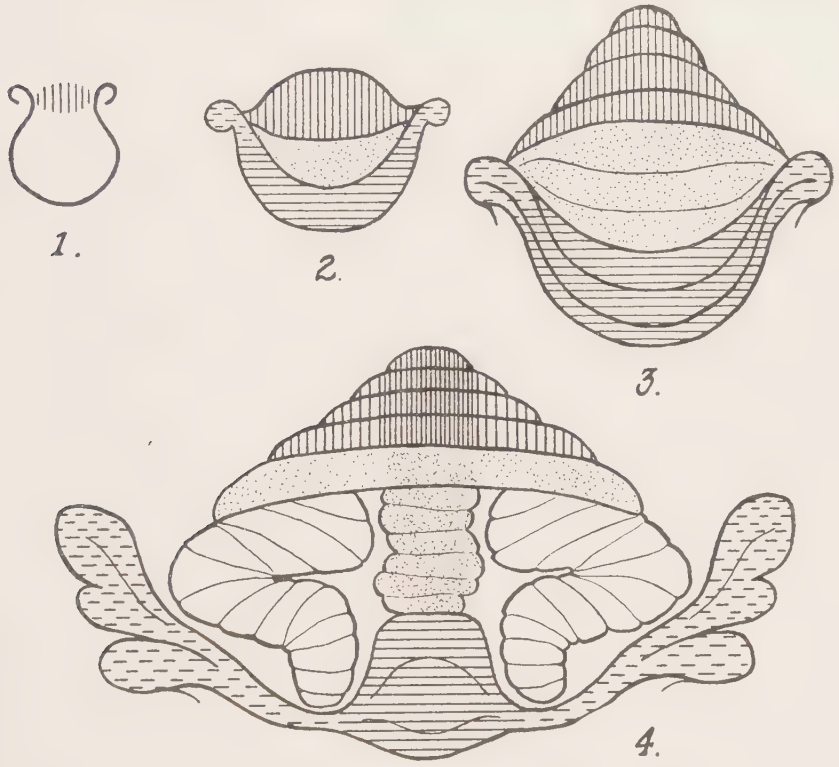

FIG. 195A. Schematic representation of the evolution of the cerebellum of: *1*, lizard; *2*, crocodile; *3*, bird; *4*, mammal. Vertical lines: *lobus anterior;* horizontal lines: *lobus posterior;* interrupted horizontal lines: *Lobulus flocculariis* of *lobus posterior;* stippling: *lobus medius;* white: *lobus ansoparamedianus*. The names of the smaller lobules of the various lobes can be identified from figure 199. (After Ingvar, *Brain*, vol. 46, p. 301, 1923.)

of Luciani and others we know that loss of the cerebellum is followed by severe motor and postural disturbances. These symptoms, however, cannot depend on the cerebellum, which has been removed, but are evoked by the rest of the central nervous system, which has been spared. *Unfortunately we know not a single function or reflex positively connected with the cerebellum, in such way that it is absent after cerebellar extirpation, and present after*

ablation of other parts of the brain, as long as the cerebellum remains uninjured. Our evidence of the postural activity of the cerebellum is purely negative. The great advantage during the investigation of the postural functions of bulb and mid-brain was, that we could there deal with positive reflexes (righting and attitudinal) which are present as long as the hind part of the brain-stem is intact. I am convinced that as soon as we succeed in finding positive reflexes connected with the cerebellum, it will be possible to eluci-

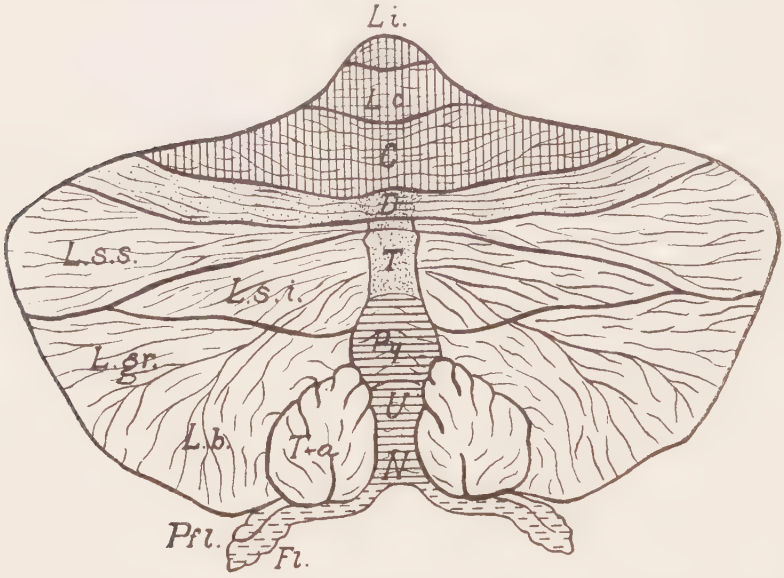

FIG. 195 B. Diagram showing Ingvar's schema applied to the human cerebellum, the subdivisions being depicted as in figure 195 A. Lettering: Li., *lingula;* Lc., *lobulus centralis;* C., *culmen;* D., *declive monticuli* (being the vermicular region of the *lobulus simplex*); T., *tuber vermis;* L.s.s., and L.s.i., *lobuli semilunaris superioris* and *inferioris* of the cerebellar hemispheres (these together constitute the "crus I" of the Bolk-van Rynberk terminology); L.gr., *lobulus gracilis;* L.b., *lobulus biventralis* (*lobuli gracilis* and *biventralis* constitute "crus II" of the above terminology, and it with crus I make up the *lobulus ansiformis* of Ingvar); T-a., *lobulus paramedianus;* Pfl., *paraflocculus;* Fl., *flocculus;* Py., *pyramis;* U., *uvula;* N., *nodulus* (the last three constitute the *lobus posterior*).

date the mystery of this undoubtedly very important part of the central nervous system. Only then can the question of the importance of the different cortical centres for posture be raised." (See also, *679*, Chapter X.) Magnus thus sheds no light upon the question of the localization of activity in the cerebellum.

What then can be the function of this extraordinary organ? The available evidence is derived from experiments involving its partial or complete extirpation, from experiments upon stimulation of various parts of the organ,

and finally from inferences drawn from its ontogeny, phylogeny, anatomical structure, and with its connections with the remainder of the brain-stem.

THE PHYLOGENY OF THE CEREBELLUM

Herrick (*465*) has pointed out that the most primitive type of cerebellum in the vertebrate scale is probably that of petromyzon. It consists of a plate developed as a direct elaboration of the lateral Deiter's area of the fourth ventricle. Histologically it contains granular cells and larger neurones similar to the Purkinje cells characteristic of the cerebellum of higher vertebrates. A spino-cerebellar tract is possibly present. As one proceeds higher into the vertebrate scale one finds the spino-cerebellar tract, together with the fibres from the vestibular nuclei, terminating in a median body which Herrick believes comparable to the vermis of higher cerebellar forms (elasmobranchs and teleosts). In reptiles the division into an anterior and a posterior lobe becomes evident, and, as Ingvar (*511*) has shown, the spino-cerebellar fibres go principally to the anterior lobe and the fibres from the vestibular nuclei exclusively to the posterior lobe. In these lower forms the afferent fibre tracts are thus similar to those found in the higher mammals. The efferent tracts are also comparable, being confined almost wholly to the superior cerebellar peduncle (*brachium conjunctivum*). In general the cerebellum increases in size as the powers for varied movements become augmented, reaching its most marked elaboration in anthropoids and man. In the higher forms of life the median lobes (including the hemispheres) have become enlarged more in proportion than have the anterior or posterior lobes.

It would not be useful to recount the varied systems of nomenclature which have been utilized in the past to describe the several morphological structures of the cerebellum. The terminology is confusing and in the following account I propose to adhere to that recently developed by Ingvar (*511*). The cerebellum by him is divided into anterior, posterior and median lobes (figs. 195A and B), the posterior lobe being subdivided into two lateral regions which are designated the flocculus and paraflocculus (fig. 199). Further description will be given below in discussing cerebellar localization.

THE CONNECTIONS OF THE CEREBELLUM

The cerebellum is in connection with the other portions of the neuraxis by three pairs of peduncles: inferior, middle, and superior. The inferior and middle peduncles are made up almost wholly of afferent tracts, while the superior peduncle, with one exception, is entirely efferent.

1. The inferior cerebellar peduncle, or restiform body, contains: (*a*) the direct cerebellar tracts whose fibres arise in the cord from the cells of Clarke's column and pass upward through the peduncle and end chiefly in the anterior lobe; this tract conveys proprioceptive impulses from the trunk and extremities. (*b*) Fibres from the gracilis and cuneate nuclei which also carry impulses of muscle sense. (*c*) Olivo-cerebellar fibres arising from the inferior olive of both sides and terminating chiefly (see *989*) in the median lobes of the cerebellum. Most of these fibres are believed to be afferent. (*d*) Fibres from the nucleus lateralis of the medulla which terminate in the cerebellar cortex on the opposite side. (*e*) Important groups of fibres from the trigeminal, facial, glossopharyngeal, vagus and probably also from the vestibular nerves. These tracts terminate chiefly in the nucleus tecti of the roof. Fibres from these cranial nerve nuclei also pass to the

cerebellum through the middle peduncle (Purves-Stewart, *786*). (*f*) There are also fibres, probably efferent, which pass to the vestibular nuclei. Finally, (*g*) there is an additional group of fibres of unknown origin which are probably afferent.

2. The middle cerebellar peduncle, or *brachium pontis*, is a continuation of the pons and carries to the cerebellum impulses arising from the pontine nuclei, which are in direct communication with the frontal, parietal, occipital, and temporal lobes of the cerebral cortex (fig. 198). By this peduncle, therefore, travel the chief efferent tracts from the cerebrum to the cerebellum. The presence of efferent fibres in the middle peduncle has not been settled, though a cerebello-tegmentalis-pontis tract has been described (Herrick, *464*, *465*).

3. The superior cerebellar peduncle, apart from the ventral spino-cerebellar tract (of Gowers) which passes into the cerebellum through this peduncle, is largely made up of efferent fibres which pass either to the red nucleus or the thalamus; some fibres also appear to pass directly to the cerebral cortex (*789*). Its chief constituents are, therefore, the cerebello-rubral tract and the cerebello-thalamic tract. The fibres passing to the red nucleus undergo decussation beneath the superior colliculus and thus establish a contralateral connection with the red nucleus. But since the rubro-spinal tract again crosses at the decussation of Forel, the cerebellum by this double decussation establishes ipsilateral control over the muscles of the body. The red nuclei, in addition to giving rise to the rubro-spinal tract, also send fibres upward to the basal ganglia and cerebral cortex (frontal lobe).

THE HISTOLOGY OF THE CEREBELLUM

This is not the place to give a detailed account of the histology of the cerebellum; adequate descriptions are to be found in any of the more detailed text-books of neurology. It will be sufficient to remind ourselves that the cerebellum differs from other cerebral structures in possessing a cortex of uniform histological structure throughout its entire extent (Ingvar, *511*). The cerebellum is composed of three layers, (*a*) an external molecular layer, (*b*) a middle granular layer, and (*c*) an internal medullary layer consisting of centrifugal and centripetal medullated nerve fibres. Between the two more external layers (the cortex) the large characteristic Purkinje cells are found. These are in dendritic communication with several morphologically different types of cell in both layers. The Purkinje cells are the only efferent motor cells of the cerebellar cortex, and consequently all impulses which leave the cerebellum must pass through them. The majority of the Purkinje fibres terminate in the deeper cerebellar structures, especially in the dentate nucleus. The efferent fibres of the superior peduncles arise chiefly in the dentate nuclei and therefore only indirectly from the cerebellar cortex.

RESULTS OF REMOVAL OF THE CEREBELLUM

We must pass over the early experiments of Flourens (*312*, 1822) and Magendie (*678*, 1824) and their immediate successors with brief mention. Flourens observed that decerebellated pigeons can neither jump, fly or walk, and Magendie found similar incoördination in dogs after removal of the cerebellum, but he discovered that decerebellated dogs were nevertheless able to swim. This led to the suggestion (Magendie) that the cerebellum is concerned more with equilibration than with coördination.

Both Flourens and Magendie, agreed that sensation was unaffected in these experiments. Cuvier (1835) anticipated more accurately the modern view in suggesting that "the integrity of the cerebellum is necessary for the proper regulation of locomotor movements." Wier Mitchell (*718*) drew attention to the increased susceptibility to fatigue after removal of the cerebellum (birds). Ferrier (see, *362*) brought forward added evidence favouring the view that the cerebellum is concerned in equilibration. Nothnagel (*736*) was the first to observe that destruction of the vermis leads to pronounced motor disturbance, while extirpation of the hemispheres produced little effect. Modern theories concerning the function of the cerebellum, however, had their origin in the experiments of Luciani, and to these we may now devote our attention. It will be most profitable first to consider Luciani's experimental results as originally set forth, and then to discuss them in the light of more recent experimental evidence.

Luciani removed the cerebellum from experimental animals under full aseptic precautions and allowed them to recover. The symptoms appearing at progressive time intervals following extirpation were divided into three periods.

1. The first period was one of "functional exaltation" ("dynamic phenomena") characterized by opisthotonus, head retraction, tonic extensor spasm with adduction, especially in fore limbs, and with recurrent alternating clonic spasms of the hind limbs. In short, the symptoms are not grossly different from those observed in decerebrate rigidity (*896*, p. 908). The animal, however, retains, though with considerable impairment, voluntary power over his muscles. Attempts to move are associated with tremor and not infrequently by simultaneous spasm of opposed muscle groups, so that locomotion is difficult and sometimes impossible. The opisthotonus and extensor spasm continue (in the absence of voluntary movement) for eight to ten days, when the second period develops. The first period of exaltation, and its original recognition by Luciani, is too often overlooked in recent discussions of the physiology of the cerebellum (cf. Starling, *964*); as we shall presently see, it is a most significant symptom of cerebellar extirpation.

2. The second period is characterized by the appearance of "deficiency phenomena" (Luciani) in which the animal exhibits an essential weakness of all his muscles. It was in this stage that Luciani recognized the three symptoms so often associated with his name (The Luciani "Triad"): (*a*) *Asthenia*, or weak motor power, especially of the hind limbs; (*b*) *Atonia*, or loss of the normal tonus of the body musculature, especially of the hind limbs, being similar to the disappearance of tone following upon posterior

root section; (*c*) *Astasia*, or the "intention tremors," and other irregularities associated with voluntary movement.

3. The final period recognized by Luciani is one of "compensation," during which the animal regains a certain measure of control over his body musculature, as recognized by increasingly successful attempts to walk. This compensation Luciani believed to be due to the development of increased power of the motor centres of the cerebral cortex, for when the cortex was subsequently removed the animal lost all power of locomotion. The stage of compensation is also seen strikingly after *unilateral decerebellation*. The immediate result of such a procedure is extensor spasticity, especially on the operated side, and a concave curvature of the trunk toward that side, (pleurosthotonus). The animal falls if locomotion is attempted, and often rolls around the long axis of its body. Tendon jerks are brisker than normal on the affected side (*302*). After one or two weeks power to walk may be regained, the fore limbs being more perfectly compensated than the hind, but tremor and lateral oscillation disturb each effort, and extensive fatigue quickly supervenes on continuance of motion. The most distressing symptoms are eventually overcome, but complete recovery was never observed, tremor being especially persistent. Such in brief outline were the symptoms of ablation of the cerebellum as first elucidated by Luciani.

In the light of more recent work, the first and third of Luciani's stages of recovery—the periods of exaltation and compensation—are deserving of especial emphasis. The *asthenia* and *atonia* of the second stage, on the other hand, have not found universal recognition in the hands of other experimenters, while the *astasia*,—"intention tremor,"—is characteristic of *all* phases ensuent upon cerebellar extirpation.

Let us first examine Luciani's interpretation of his observations on the symptoms following cerebellar extirpation. He attributed the first stage, that of "dynamic phenomena" or exaltation, to irritation and possible vertigo ensuent upon the trauma of the operation, pointing out that many of his dogs gave evidence of prolonged inflammatory reaction under the best of aseptic conditions. The extensor rigidity he was inclined to regard as due to persistence of stimulation set up by inflammation, and only after this subsided did the true effect, namely generalized weakness, etc., appear. Sherrington (*896*, 1900) early pointed out the inadequacy of this explanation on the grounds: (*a*) of the effect being too long continued (eight to ten days) to be due to irritation, and (*b*) irritation when set up mechanically or electrically in certain regions of the cerebellum or cerebellar peduncle gives rise to *inhibition* of tonic contraction rather than to spasticity as one would

expect from Luciani's explanation (see below). A similar conclusion was reached in 1902 by Lewandowsky (*628*). Sherrington emphasized that the removal of the cerebellum gives rise to symptoms (*e.g.*, increased knee-jerks) which are much more characteristic of a "release" phenomenon, such as one finds in the case of decerebrate rigidity, than of an irritational effect. This explanation is in keeping with the more recent experimental evidence.

When we come to Luciani's second stage characterized by what he terms "deficiency phenomena" with his triad of symptoms, asthenia, atonia, and astasia, it is also somewhat difficult to accept his interpretation, especially in view of more recent work. In the first place, weakness, or asthenia, has *not* been found to characterize experimentally decerebellated animals in which the operative procedure has not damaged or led to "softening" of the underlying nuclei in the fourth ventricle (Dusser de Barenne, *256;* and Magnus, *679*). Also the hypotonia upon which Luciani placed so much emphasis has not found universal recognition, especially in the hands of Dusser de Barenne. This author has given the following illuminating description of his decerebellate cats and dogs (*256*).

As in Luciani's animals, there appeared immediately after the operation the dynamic period characterized by pronounced opisthotonus and rigidity of the extremities, especially of the fore limbs. In the course of several weeks this period was observed to progress gradually and almost imperceptibly into the stage of compensation, without passing through an intermediate period of weakness. In fact, no evidence was found either of atonia or essential asthenia. The extreme opisthotonus diminished after two days. The head in all stages was held symmetrically with the body; there was *no* nystagmus and no difficulty in swallowing. After 3 or 4 days the animals were able to lie flat on their bellies more or less symmetrically. Within 7 or 8 days they were usually able to stand on their four legs, but only after considerable effort accompanied by extreme tremor. After about 10 days the animals were sometimes able to push themselves along by sudden jerks of their hind limbs while their fore limbs slid over the ground like two rigid stilts. Their progression was thus discontinuous and sporadic. Sensory functions and comprehension remained normal, the animals attempting quickly to obey commands. Their locomotor powers improved gradually but never completely, pronounced dysmetria remaining as a permanent symptom. Swimming movements were not carried out normally (cf. Luciani). Under certain circumstances, however, the dysmetria did not show itself, namely, in reflexes such as scratching (dog), which are more or less spinal in character. Cats did not show it when "washing" their snouts or licking their body. The "classical" symptoms of

atonia and nystagmus, when they occur, would appear in the light of these results to be caused by involvement of some structures *other* than the cerebellum.

Dusser de Barenne writes: "I believe in accordance with my experimental experience, that in successful operations, where there are no secondary lesions of other parts of the central nervous system and no infections, etc., that there, atonia in the sense of Luciani is absent, as well as asthenia. The first stage after total extirpation of the cerebellum is as you have quoted; the time that the opisthotonus is to be observed differs somewhat from animal to animal. I have seen it beginning to disappear already slightly two days after the operation. The hypotonia in most clinical cases is, I think, due to shock or diaschisis of other systems, for as a matter of fact you see it in tumours and other acute destructive lesions (abscesses, haemorrhages), but not in cases of cerebellar atrophy."

One feature which all investigators have recognized is the tendency for the initial symptoms to become modified or, as Luciani expressed it, "compensated." Among clinical observers there is unanimity of opinion that hypotonia is observed in late (and possibly in early) cerebellar disease, especially in extensive cerebellar tumors, and it was also a prominent symptom in patients with gunshot wounds involving the cerebellum, as noted by Gordon Holmes (*497*) in his extensive war material. Are we therefore to suppose that atonia is a primary result of impaired activity of of the cerebellum, or may it be due to some secondary effect such as a "compensation" by other portions of the nervous system (*e.g.*, the cerebrum), or to some primary involvement (by pressure) of other medullary nuclei concerned in the maintenance of tonus? In clinical material it is of course notorious that the impaired activity is ordinarily the result of slow process, for, except in sudden haemorrhages (which by repercussion usually also involve underlying structures), cerebellar lesions develop gradually. In animals where this organ can be removed suddenly there is unanimous agreement that symptoms of "hyper-" not "hypotonus" are the immediate result (Sherrington, *886*, p. 327). As early as 1894 Ferrier and Turner had observed the prolonged augmentation of the knee-jerk (monkeys) following cerebellar extirpation, and they suggested, in view of the belief that the knee-jerk is an index of tonus, that this indicated a condition of hypertonus rather than one of atonia. As experimental surgical technique has become improved, the duration of the period of heightened tonus has become lengthened, although in any given animal its severity tends progressively to diminish with lapse of time. On these points there is no dispute. Our difficulty comes when we attempt to account for the clinical symptoms of atonia and for the similar condition which early authors found in experimental animals.

If one inquires into the reason for this discrepancy between recent experimental results and the time-honoured clinical picture, the following considerations suggest themselves. Successful surgical removal of the cerebellum leaves no débris behind and does no injury to the underlying vestibular nuclei. Clinical lesions (or experimental lesions when followed by haemorrhage) are almost invariably associated with a rise of intracranial pressure, and, in addition to this, tumour growths not infrequently cause *local* pressure in the vestibular region of the medulla (*256*). Any factor which interferes with the activity of the vestibular nuclei causes hypotonia and weakness (*679, 788*). We shall see in the following chapter that the vestibular nuclei "protect" the anterior horn cells from inhibitory stimuli arising locally. I would urge with Dusser de Barenne that the cause of hypotonia in the majority of cerebellar lesions observed clinically (and in early experiments) is due, not to primary cerebellar impairment, but to involvement of the vestibular nuclei. This would release the lower inhibitory arcs and thus lead to an obliteration of the normal myotatic reflexes responsible for the maintenance of tonus (see Chapter XXI).

CLINICAL SYMPTOMS OF CEREBELLAR DISEASE

Save for the symptom of hypotonia, clinical and experimental results of cerebellar lesions are in substantial agreement. This is not the place to describe extensively the symptoms of cerebellar disease (for which one may consult especially Gordon Holmes, *497*). We may note, however, that the two most pronounced symptoms are tremor, which is predominantly an intention tremor, being more marked the more strongly "willed" the action, and ataxia of which the most distressing aspect is the tendency for incoördinated contraction of various antagonistic and synergic muscle groups. A man with even slight involvement may, as he progresses, reel like a drunkard; the dog with a cerebellar lesion may similarly reel and stumble and fall, often several times in traversing a distance of a few feet to obtain his food. There is no great discrepancy here between the pathological and the experimental lesion.

The other clinical symptoms are *dysmetria*, or misjudgment of distances in willed movements, which probably owes its existence to the inability to inhibit a movement once it is started. The inhibitory "brakes" are, so to speak, absent when the activity of the cerebellum is impaired. Dysmetria was originally attributed by Luciani to *atonia*, the antagonist not offering sufficient resistance to contraction of the protagonist, with the result that the latter overshoots its mark. This theory has also been invoked by Walshe (*1021*) to account for various similar features of the clinical picture.

Such an explanation would appear to be excluded, however, by the fact that dysmetria is a pronounced symptom during the dynamic period of hypertonus, and also by the fact that atonia is not an essential concomitant of experimental decerebellation. The same conclusion has been reached on other grounds by Mills and Weisenburg (*715*). Another symptom, which probably also is a manifestation of dysmetria, has been described by Babinski (*42, 43*) and termed *catalepsy;* that is, the tendency to maintain an attitude longer than does a normal subject. An additional clinical symptom upon which much emphasis has been placed is the *adiadochokinesis*, or the inability to perform rapidly such alternate movements as pronating and supinating the arms (*41*). There is also the tendency for *decomposition* of movements, that is, a single act, such as touching the right knee with the left heel, will not be performed directly but will be split up into two separate motions, *e.g.*, as drawing the right leg gradually up along the left leg and then subsequently lifting it, usually rather awkwardly, on to the left knee. This symptom may, however, be due to the essential atonia (as suggested by Purves-Stewart, *786;* see also *1021*), and if this is the case, it is probably not part of the pure cerebellar picture. The so-called "pass-pointing" (Bárány), or the tendency for the extended arm to wander when the eyes are closed, is also an important clinical symptom, especially as corresponding movements are observed in hemidecerebellate animals.

Save for the atonia, it is evident that all the clinical symptoms are in perfect keeping with what one would anticipate from the symptoms following experimental cerebellar extirpation in animals. They are in keeping, moreover, with the belief that the cerebellum is the "head ganglion of the proprioceptive system." It is true that the vestibular reflexes and the tonic neck reflexes occur in the absence of the cerebellum which demonstrates that important proprioceptive centres or "ganglia" must also exist elsewhere in the mid-brain, but this does not mean that postural responses are not influenced in a normal animal by the presence of the cerebellum. The fact that the righting and attitudinal reflexes become augmented on decerebellation shows that normally this organ exerts control over them. Voluntary activity can still be accomplished without the cerebellum, but it is accomplished uneconomically and with great difficulty, and this may also be true of the postural reflexes. However, we need to know more concerning the reactions of decerebellated thalamic animals, in which cerebral influence is excluded, before conclusions can safely be drawn.

ELECTRICAL STIMULATION OF THE CEREBELLUM

Space forbids a complete history of the controversy concerning the electrical excitability of the cerebellum. A résumé has been given by André-Thomas (*27*) and by Miller and Banting (*713*). It is sufficient to say that certain of the earlier experimenters did not guard against spread of stimulating current (to the underlying structures of the fourth ventricle and especially to the nervus accessorius) and their results were therefore often not genuine effects of cortical stimulation (see Horsely and Clarke, *499*). Sherrington, however, noted in 1898 (*886*) that if the anterior surface of the cerebellum is faradized, even weakly, in a decerebrate preparation, the rigidity became inhibited on the homonymous side, and he described the inhibitory area as extending over the anterior surface of both the vermis and the lateral hemispheres. This observation has recently been independently[2] confirmed by Bremer (*146*) and by Miller and Banting (*713*). The latter authors described the limit of the inhibitory area of the vermis as extending from its most anterior portion to about 3 mm. above the medulla (cat) posteriorly, and for several millimetres laterally on either side of the vermis. They noted that inhibition could be detected in all four legs when the vermis was stimulated, and they emphasized that success of the experiment depends upon ensuring an adequate circulation in the region stimulated. Bremer, in an extensive investigation in which myographic records were obtained (see fig. 196), set approximately the same limits upon the inhibitory area anteriorly as that described by Miller and Banting, but he emphasized that the pyramis and floccular regions also produce inhibition. Bremer insisted, moreover, that the remainder of the cerebellar cortex (especially the hemispheres, yields no response whatsoever when stimuli of moderate intensity are employed.

Thiele (*977*), Cobb, Bailey and Holtz (*206*), Miller and Banting (*713*) and Bremer (*146, 147*) all observed that the superior peduncles also give rise to inhibition of decerebrate rigidity when stimulated. It is, however, important to recognize that the "decerebrate" preparations used in these experiments were "acute" preparations sectioned above the level of the red nucleus. In *chronic* animals sectioned at this level the distribution of tonus, as Rademaker (*788*, see also *679*) has so conclusively demonstrated, is normal with relation to the flexors and extensors of the body, though it

[2] Miller and Banting brought forward their results in December 1921 at the *American Physiological Society* (preliminary note published in February 1922), while Bremer communicated his preliminary results to the *Societe de Biologie* on April 29, 1922 (see *Comptes Rendus*, tom. 86, p. 955).

may occasionally be somewhat heightened in both groups of muscles. However this may be, those who have studied acute decerebrate preparations sectioned above the level of the red nucleus are familiar with the fact that pronounced extensor rigidity not infrequently develops (though it

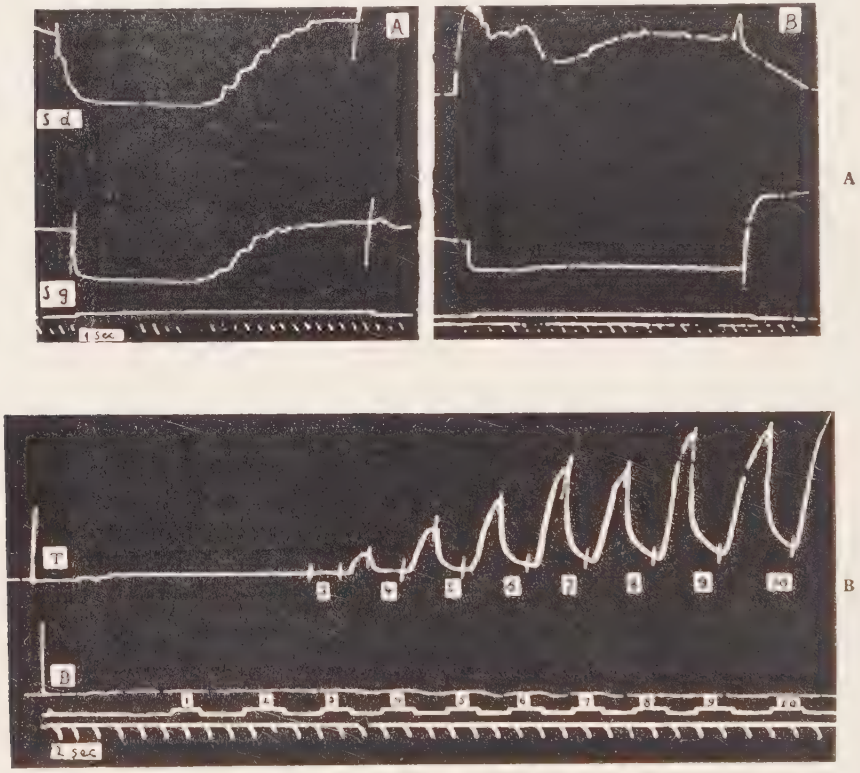

FIG. 196 A. Relaxation of a tonic muscle produced by stimulation of the vermis of the cerebellum.

B. "Rebound" of the triceps and biceps of a decerebrate cat following stimulation of the "inhibitory" region of the cerebellum at a point 3 mm. to the left of the midline of the vermis. Since the muscles were toneless, the initial inhibitory relaxation is not shown. Intensity of stimulus the same throughout (8 cm.); consequently this record also illustrates the phenomenon of facilitation. (From Bremer, *Arch. Int. Physiol.*, tom. 19, p. 222, 1922.)

always becomes more marked if the red nucleus is interfered with by sectioning the brain-stem a few millimetres more distally). In acute "red nucleus animals," therefore, one has a background of extensor tonus by which to

estimate the inhibitory effect of cerebellar stimulation; and there can be no doubt that stimulation of the superior peduncles, as well as the limited region of the cortex already described, gives rise to inhibition of tonus. That it is an inhibition comparable to that which occurs on stimulating an ipsilateral sensory nerve, is evident from the fact that it is characterized by post-inhibitory rebound as well as facilitation,—an important observation for which we are indebted to Bremer (see fig. 196 B). Bremer has also described the noteworthy fact that as one irritates the superior peduncle mechanically, as by section with a knife, inhibition also results. As he remarks, "La section isolée des pédoncules cérébelleux supérieurs peut provoquer une abolition très transitoire de la rigidité, due sans doute à l'excitation par la section des fibres inhibitrices contenues dans ces pédoncules" (*147*, p. 202; see also *896*, p. 906, footnote 3).

It must not be assumed from this evidence that the superior peduncles contain nothing but inhibitory fibres. It is only safe to infer that, as in a mixed ipsilateral nerve, inhibitory effects predominate when tested against pre-existing contraction in an extensor muscle. Some authors (*206*, *713*, *146*) have noted that peduncular stimulation and stimulation of the vermis caused "walking" of the limb muscles as a rare alternative to the usual inhibitory effect. Since rhythmic activity is a characteristic feature of simultaneous stimulation of excitatory and inhibitory nerves, it is reasonable to believe that the efferent fibres from the cerebellum are, with respect to the extensor muscles, a mixture of excitatory and inhibitory fibres in which the inhibitory fibres predominate.

Stimulation of the vermis, however, gives rise to "pure" inhibition, as is shown by the fact that it is not "reversed" by generalized strychnine poisoning (*147*). But for reasons already mentioned, this does not mean that *all* fibres passing from the superior peduncles are, with reference to their effect on extensor tonus, purely inhibitory. Fibres originating in other (deeper) parts of the cerebellum may give rise to excitation. Miller (*712*) has recently made the important observation that whereas local application of strychnine to the inhibitory area of the cerebellum causes an increase in the decerebrate rigidity, especially of the fore limbs, it does not destroy the power to evoke inhibition by faradic stimulation of this area. This interesting result may possibly be accounted for by the assumption that strychnine tends to cause a withdrawal of the normal inhibitory influence exerted by the cerebellum.

There exists some uncertainty as to the precise pathway by which the inhibitory impulses pass from the cerebellum to the spinal centres. The cerebello-rubral tract takes origin in the dentate nucleus of the cerebellum and the portions of the cerebellar cortex which give rise to inhibition do not communicate with the dentate nucleus but with the underlying roof nuclei. It would appear from this that the inhibitory impulses pass from the palæocerebellum via the roof nuclei and then by some as yet undiscovered tract to the red nucleus. Bremer (*147*) supposes the existence of what he has termed a fastigio-rubral

tract, but as he points out the existence of this was not recognized by van Gehuchten (*392*, see also Allen, *23a*). The fact remains, however,—having been first satisfactorily demonstrated by Cobb, Bailey, and Holtz (*206*) and confirmed by Bremer (*147*),—that the inhibitory effect of stimulating the cerebellar peduncles immediately disappears if the red nucleus is excluded by section of the brain-stem. One cannot therefore avoid the conclusion that the inhibitory impulses pass to the spinal centres *via* the red nucleus, but the precise anatomical pathway from the cerebellum must be left an open question.

THE RELATION OF THE CEREBELLUM TO THE RED NUCLEUS AND TO DECEREBRATE RIGIDITY

The efferent fibres in the superior peduncles of the cerebellum are, as we have seen, composed chiefly of two groups, those going to the red nucleus and those to the thalamus and basal ganglia. In sectioning the brain-stem above the level of the red nucleus, one has "released" that centre from the control normally exerted upon it by the basal nuclei. In the chronic animal true decerebrate rigidity of the extensor type does not, however, develop as a result of section above the red nucleus. It tends to develop, however, if the superior peduncles of the cerbellum are cut. This is a point which has been emphasized by Bremer (*217*). In other words, an important part of the sustaining effect upon the distribution of tonus exerted by the red nucleus is due to its connection with the cerebellum. When this inhibitory control is removed, extensor spasm ensues. However this may be, exclusion of the red nucleus in a decerebrated animal causes the symptoms of rigidity to become even more pronounced. It would therefore appear that the red nucleus is under control from sources other than the thalamus and the cerebellum. It is possible that some of the ascending proprioceptive tracts from the cord emanating from the extremities or from the neck muscles exert a direct influence on the red nucleus, but as yet there is to my knowledge no anatomical basis for this assumption.

The red nucleus has an interesting phylogenetic history. In the lower vertebrates it is composed of large neurones which give rise to the rubrospinal tracts. In mammals, however, as von Monakow (*720*) has pointed out, a second newer portion of the nucleus has developed which histologically is composed of small cells, and by Hatschek (see *60*) has been called the *nucleus parvicellularis*. This latter nucleus has developed in association with the development of the thalamus and cerebral cortex and is connected with them. In consequence of this the newer part of the red nucleus is in man and apes its largest portion, while the giant-cell part has become very much diminished with a resulting diminution in the rubrospinal tract. However this may be, owing to the great increase in size of the small celled part in man, the red nucleus is very much larger than that of the cat even when allowances are made for the differing diameter of the mid-brain in each species (*720*). The new part of the red nucleus, in addition to its connection with the higher centres, is also, according to von Monakow (*720*) and Allen (*23a*) in close relation with the cerebellar fibres which pass to the red nucleus via the superior peduncle.

Other tracts converge upon the red nucleus but the cerebellar and the thalamic tracts are clearly the most important. Monakow (*720*) describes, however, a fronto-rubro-tegmental pathway. Also Wilson (see *60*) finds a large tract of fibres from the globus pallidus of the lenticular nucleus which passes to the red nucleus. The efferent fibres which pass from the red nucleus are those composing the rubrospinal tract and, as we have already noted, these have their origin in the older part of the nucleus which is composed of giant cells. We may thus consider the red nucleus most conveniently as a double organ having a "cerebellar centre" and a "basal ganglia centre."

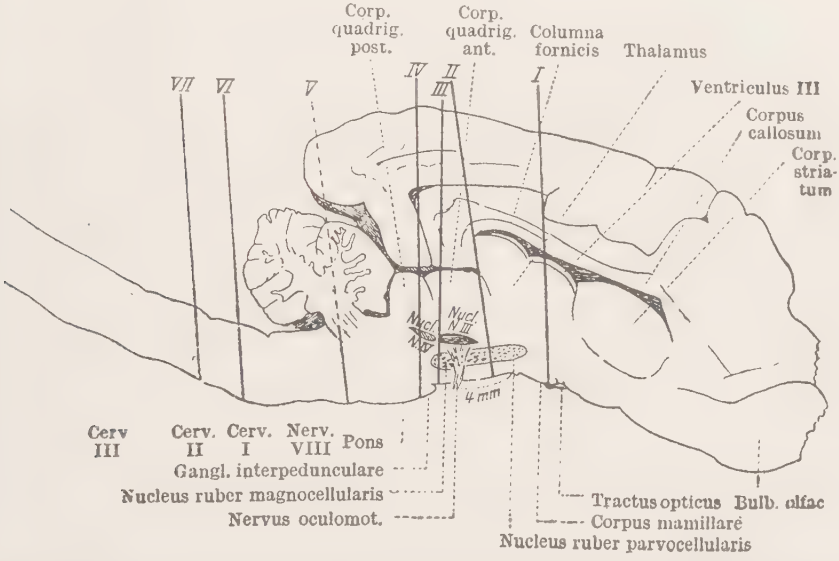

FIG. 197. Magnus's diagram showing the various levels of transection (cat) of the brain-stem used in his and Rademaker's analysis of the distribution of tonus. Further details given in the text. (*Körperstellung*, p. 601, 1924.)

Investigations of Rademaker and of Magnus upon the Red Nucleus. Within the past two years new light upon the function of the red nucleus has been provided by Rademaker (*788*) and Magnus and Rademaker (*682*) in their exhaustive experiments upon the relation of the higher centres to the postural reflexes. They have found that the red nucleus when intact and functional gives to an animal normal distribution of tonus. They sectioned the brain stem at various levels and studied with great care the various neck, labyrinthine and righting reflexes at each successive level, and in Magnus' words, they have made a beginning "towards translating the physiological facts into anatomical language" (*680*, p. 351). In figure 197 is shown the various levels at which sections of the brain stem were made

in Rademaker's experiments. We may refer to the sections indicated in the diagram as Sections I, II, III, etc., in this way avoiding lengthy anatomical definitions. It will be seen that the first section passes in the region of the thalamus and gives the so-called "Magnus" or "thalamus" animal.

Section I (*the "Magnus" or "thalamus" animal*). The plane of the section is from the mid-thalamic region dorsally to the anterior border of the corpus mamillare ventrally. This preparation is characterized by what Magnus has called "Sprungbereitschaft," and also, the power of simple coördinated reactions (walking, running, or jumping). It is possessed of all four postural righting reflexes, and, in addition, the distribution of tonus is "normal," *i.e.*, there is no extensor rigidity, and both flexors and extensors on passive movement of the limbs exhibit tonus of usual intensity. When left to itself the thalamus animal often remains in a sitting position motionless; it can, however, be stimulated by auditory and skin stimuli to locomotor activity, which is normal and carried out with perfect coördination. Periodically (*e.g.*, at 10 minute intervals) vigorous walking and running movements occur which appear to be initiated spontaneously (Schaltenbrand und Girndt, *849*). When overturned the animal rights itself, etc. The thalamus animal has the power of temperature regulation. This animal also possesses the positive and negative "supporting reactions" recently described by Magnus (*681*).

Section II (*the mid-brain animal*). This section passes just in front of the mid-brain so as to spare the red nucleus. Such a preparation has normal distribution of tonus, *i.e.*, it exists (as in the intact animal) in both extensor and flexor muscles; postural righting reflexes are present, as is also the "liftreaktion" (flexion of the limbs and lowering of the head when the animal is lifted vertically through space, and extension of limbs and lifting of head when it is lowered). The mid-brain preparation differs from the Magnus animal, in that it has no power of temperature regulation, and it does not exhibit periodic rhythmic movements. Probably as a result of the absence of the temperature mechanism the mid-brain animal tends to deteriorate more rapidly than the thalamus and under such circumstances shows mild degrees of heightened extensor tonus. This Magnus and Rademaker attribute to interference with the red nucleus.

Section III. Division of the brain stem at this level (which just excludes the red nucleus) gives to the animal the characteristic features of decerebrate rigidity. The distribution of tonus is no longer normal but is an exaggerated caricature of normal standing, in which the extensor muscles are ridigidly contracted and the flexor muscles are practically without tonus. The righting reflexes are destroyed by the destruction of the red nucleus.

but the simple labyrinthine and neck reflexes affecting the body musculature are still present.

Section IV. This section passes through the posterior corpus quadrigeminum and differs from the preceding section only in the greater tendency for fluctuation of the rigidity.

Section V. This passes just above the level of the vestibular nuclei. So long as the activity of these nuclei are not interfered with by the operation the tonic labyrinthine and neck reflexes present still remain and the head lowering reaction is present.

Section VI. The tonic neck reflexes still show themselves on the extremities provided the level of section is above the first cervical root, but decerebrate rigidity is of course absent.

Section VII. When below the level of the second cervical the tonic neck reflexes are abolished and the true spinal animal results.

The observations of the Utrecht School are thus in essential harmony with those of Bazett and Penfield (*60*), but greatly amplify the observations and conclusions of these investigators. Magnus and Rademaker's insistence that the red nucleus provides normal distribution of tone and that it is the centre necessary for all righting reflexes (except the cortical eye centres) is of great importance and supercedes all previous observations on this question. It had been known that alteration of the level of transection greatly altered the extent of the rigidity present, but to Rademaker and Magnus we owe the proof that it is the red nucleus which causes these marked alterations. We can not enter here into a description of the beautiful experiments of Magnus and his collaborators. They have been described at length by Magnus in his exhaustive monograph (*679*) on the postural reflexes, and a useful resumé of his work is to be found in the Croonian Lecture for 1925 (*680*).

THE RELATION OF THE CEREBELLUM TO THE CEREBRAL CORTEX

The extensive efferent connections between the cerebrum and the cerebellum suggest that these two important organs of the brain are intimately related functionally. We have seen that various portions of the cerebrum send large fibre tracts to the pontine nuclei, which in turn have extensive contralateral connections with the cerebellum through the middle peduncle. Consequently the crossed cerebellar hemisphere must be directly influenced by the cerebral cortex. Sherrington early pointed out that after severing both the superior peduncles and the tracts from the cerebrum to the pontine nuclei, decerebrate rigidity set in, the symptoms of which closely resemble those following removal of the cerebellum. This naturally emphasizes the

importance of the cerebro-cerebellar connections. It is also important to realize that, by the decussation of the pyramidal tracts and the further decussation of the ponto-cerebellar connections, "one and the same cerebral discharge" may reach the crossed final common path both directly and mediately through the cerebellum (fig. 198).

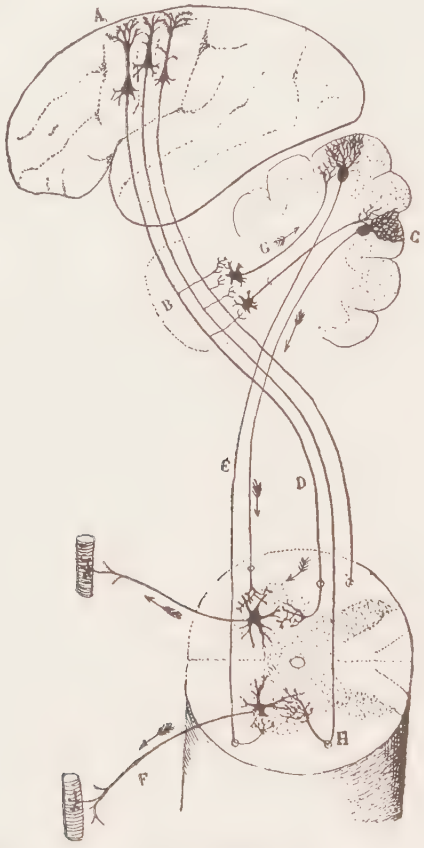

FIG. 198. A diagram illustrating the interrelation of the more important cerebral and cerebellar motor pathways. Lettering: *A*, motor area of the cerebral cortex; *B*, cortico-ponto-cerebellar tract; *C*, cerebellar cortex; *D*, cortico-spinal tract; *E*, cerebellar-spinal tract, axons of Purkinje cells of cerebellar cortex; *F*, neurones of the final common path; *G*, middle cerebellar peduncle. (Ramon-y-Cajal, *789*, tom. 1, p. 547, 1908.)

The experiments of Weed (*1037*) and of Olmsted and Warner (*739*) indicate that part at least of the cerebral pathways which cause inhibition of decerebrate rigidity, pass through the cerebellum. Thus, Weed observed in a hemi-decerebrate and in ordinary

decerebrate preparations that an inhibitory path could be traced from the cortex down the mesial anterior limb of the internal capsule into the mesial portion of the crura cerebri. He believed that the fibres ended in the pontine nuclei, for stimulation of this region and of the middle peduncles in the cerebellum produced inhibition of rigidity comparable in intensity to that evoked from the internal capsule. Olmsted and Warner believe that they have found the origin of this cortico-cerebellar pathway, for in their hands decerebrate rigidity ensues when a small region in the frontal area of the cortex is destroyed. Moreover, when this region is subsequently faradized, the rigidity diminishes. Doubt has been expressed by McCouch (personal communication) as to the precise site of origin of these cortico-inhibitory fibres, since rigidity has not, in his experience, invariably occurred after removal of the area defined by Olmsted and Warner. However, there can be no question of the existence of an inhibitory pathway from the cortex to the cerebellum, which passes along the internal capsule and (after a synapse in the pons) into the middle peduncle of the cerebellum. However, Weed's belief that the cerebellum is necessary for the maintenance of decerebrate rigidity has been controverted by all subsequent experimenters (*e.g.*, Magnus, *679*, Chapter X).

The question of the existence of cerebello-cerebral tracts still remains open; that is, there appears to be no direct anatomical proof that the cerebellum sends fibres to the cortex, but the thalamic connections suggest that cerebellar impulses influence the cerebrum through the basal ganglia. However, there is abundant physiological evidence that excitation of the cerebellum may recoil by way of the superior peduncle back to the cerebral hemisphere. Rossi (*823*), for instance, has substantially confirmed Russel's (*830*) evidence of a normal reinforcing action of the cerebellum on the cerebrum, for he observed that removal of one lateral cerebellar hemisphere in the dog caused in the opposite cerebral cortex (motor area) an immediate diminution of excitability which was followed by an augmentation. In a later paper (*824*), Rossi also observed that faradic stimulation of an intact cerebellar cortex (which is inexcitable as judged by its direct motor effects, see above) increased the excitability of the cerebral motor area of the opposite side. As Rossi points out, this adds further evidence to the view that the cerebellar cortex is excitable. He did not find, however, any evidence of localization of effect; a general augmentation of excitability of the motor area was observed wherever the cerebellar hemisphere happened to have been stimulated. This we believe supplies ample evidence, if indeed evidence is needed, that the cerebrum and the cerebellum are in intimate functional union in the normal animal. "No fact is clearer in the physiology of the central nervous system than that many movements of great taxic complexity, *e.g.*, of progression, etc., can be carried out in a coördinated manner in the absence of the Rolandic cortex and of the cerebral cortex altogether. It is also clear that lesions of the cerebellum greatly disturb these movements." This further emphasizes the functional importance of the cerebellum in facilitating orderly and delicately adjusted movements.

THE PROBLEM OF CEREBELLAR LOCALIZATION

The discovery of localized areas in the cerebral cortex which when stimulated give rise to movement of various muscles of the body, led to the search for similar areas of functional localization in the cerebellum. It had been recognized that each lateral half of the cerebellum was functionally associated with the corresponding half of the body, *i.e.*, its control was homonymous. The further development of experimental evidence was fraught by many difficulties, not the least of which was that of the gross morphological structure of the cerebellar organ itself. Consequently, in order to discuss the problem of cerebellar localization we must first consider the problem of its structure. Probably the most satisfactory division of the cerebellar lobes is that worked out by Ingvar on the basis of comparative anatomical studies. As his divisions have been widely accepted, it will not be necessary to discuss the older classifications.

Morphological divisions and the distribution of afferent fibre tracts of the cerebellum. In a carefully developed argument Ingvar has emphasized that the cerebellum is most profitably subdivided on the basis of the region of termination of its afferent connections, and he emphasized the three following considerations as essential to an understanding of the significance of this distribution. (*a*) The cerebellum is of similar structure throughout its entire extent, *i.e.*, in all parts of the organ one observes the same histological layers; (*b*) it is built in the same manner in all the higher vertebrate forms, possessing obvious homologies; (*c*) in every animal the cerebellum appears above the vestibular nerve, and he urges that this cannot be a mere accident of ontogeny. "Naturally all these facts indicate a uniform function in all animals and a uniform function in all parts of the cerebellar cortex, but they do not exclude a localization of function."

Ingvar points out that any cerebral organ in process of evolution develops within its central regions rather than along its margin, and he brings forward cogent reasons for believing that the most anterior and the most posterior portions of the cerebellum are phylogenetically the oldest, while the central, or median, portion is a more recent development. To the latter, therefore, he applies the term of "neocerebellum" and to the former "palæocerebellum." On the basis of these generalizations the cerebellum is divided into an *anterior lobe* which includes all portions of the organ anterior to the sulcus primarius; into a *posterior lobe* which includes the pyramis nodulus and uvula (*i.e.*, the posterior segment of the vermis), together with the two lateral floccular formations (flocculus and paraflocculus); the remainder of the cerebellum constitutes the *median lobe*. This includes the *lobus simplex*, and the larger portion of the cerebellar hemisphere (the two *lobi ansoparamediani*). Ingvar's division is shown diagrammatically in figure 199.

In justification of this division Ingvar points out that the most anterior part of the anterior lobe (the lingula) and the most posterior portion of the posterior lobe (nodulus, uvula and flocculus) are the regions of termination of the afferent tracts from the vestibular nuclei, and since the cerebellum is primarily an outgrowth of these nuclei, these are the oldest regions. The region of termination of the spino-cerebellar tracts is also confined chiefly to the anterior and posterior lobes, as shown in figure 199. The vertical lines in this figure show the endings in the cerebellar cortex of the spino-cerebellar tracts. It will be

seen that the spino-cerebellar tracts terminate in the lateral, so-called paraflocculär lobules and also extensively in the anterior lobe. None of the afferent tracts from the cord have thus far been traced to the ansiform lobes.

The median lobe, on the other hand, which reaches its highest development in man, is a late addition in the phylogenetic scale and receives its afferent supply from the middle cerebellar peduncles which also are found only in the higher animals. These peduncles carry to the cerebellum numerous fibre tracts from the cerebral cortex (through the pontine nuclei) and cannot therefore be expected to exert a direct control over the body musculature. However this may be, it is universally accepted that the hemispheres (lobi ansoparamediani) are in functional relation with the extremities, and all authors are agreed that the levels of the spinal cord are not segmentally represented in the cerebral cortex, rendering it highly probable that these regions are correlated with the body musculature

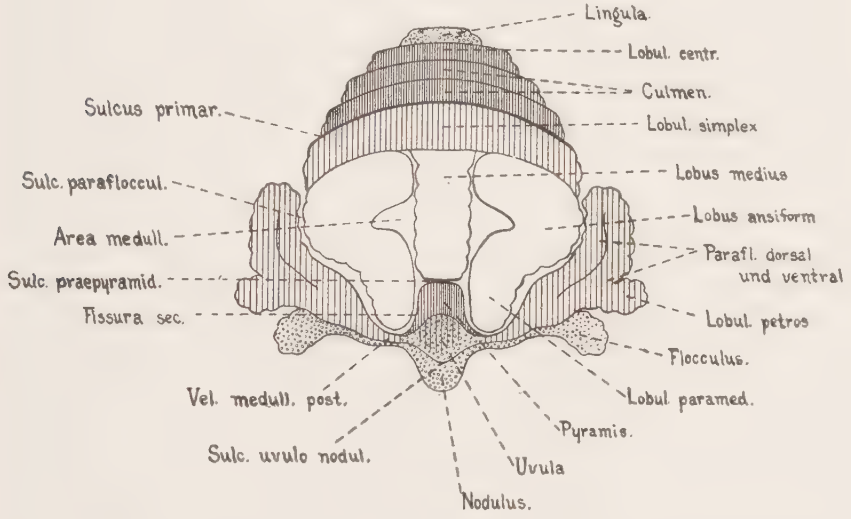

FIG. 199. Schematic representation of regions of termination of direct vestibulocerebellar fibres (small circles) and spinocerebellar fibres (vertical lines) in the cerebellar cortex. (Ingvar, *Brain*, vol. 46, p. 301, 1923.)

en masse, and that these lobes therefore behave as functional units. Stimulation of the hemispheres, as we have seen, has been found ineffective, save as it influences the cerebral hemispheres.

It will be recalled that Bolk (*124*, *125*) elaborated a speculative scheme of localization based on comparative anatomy. He, for example, urged that the "coördinative centre" for the neck muscles was situated in the lobulus simplex because this lobe was small in the mole and ant-eater and large in the giraffe. Though always suggestive, this form of argument had not met with universal approval, especially when applied to other cere-

bellar "centres" in which the anatomical differences are less well defined. Bolk's scheme of localization may be found in many text-books, but in its literal interpretation it is now of little more than historical interest. There is, nevertheless, an important body of experimental evidence tending to show that certain parts of the cerebellum have more to do with certain anatomical portions of the body musculature than other portions of this organ, and to this we must now direct our attention.

Bremer (*147*) has made the important observation that the zones of the cerebellum from which inhibition of extensor tonus is to be elicited corresponds closely with the region of termination of the spino-cerebellar fibres as established by Ingvar (fig. 199). In his words, "Il faut signaler ici une coincidence remarquable: la topographie de ces deux zones excitables correspond exactment aux deux territories de réception des fibres proprioceptives spino-cérébelleuses, ainsi, qu'ils ont été établis par des travaux concordante de MacNalty et Horsley et récomment Ingvar, chex le chat." This indicates that the cerebello-inhibitory fibres take origin from the region of termination of the proprioceptive afferent fibres of the cord, and it has thus an important bearing upon the problem of higher coördinative control discussed in the following chapter. It is clearly a point of importance that the ascending tracts from the muscles are associated with fibre groups which lead to inhibition of such myotatic phenomena as decerebrate rigidity, and lends strong presumptive evidence in favour of our thesis that removal of the cerebellum leads to symptoms characteristic of release from inhibitory control (Bremer).

It may be pointed out in this connection that the results of severing the inferior peduncles lead to dynamic phenomena less marked than, though in many respects similar to, those observed on severing the superior peduncles (*896*, p. 901). Moreover, Bing (see *147*) has observed that simple lesion in the cord of the ascending spino-cerebellar tracts (Flechsig and Gowers) gives rise to symptoms (homolateral) of dysmetria and abnormal posture more or less suggestive of the clinical cerebellar picture. Bremer (*147*) stimulated these ascending tracts and observed inhibition of rigidity, but this still occurred after section of the superior cerebellar peduncle, which suggested that part at least of the inhibitory effect was extracerebellar.

van Rynberk (*835*) in a prolonged series of experiments has obtained highly important evidence relating to cerebellar localization. He has observed that extirpation of the lobulus simplex profoundly modifies the behaviour of the neck muscles, causing head nystagamus and a tendency to fall backwards, but there is also involvement of the limb muscles (see Grey, *410*, and Greggio, *409*). Destruction of the anterior portion of the median lobe ("crus I") gives rise to predominating ipsilateral symptoms in

the foreleg, while destruction of certain portions of the posterior part of the median lobe ("crus II") leads chiefly to weakness of the ipsilateral hind leg. For further details one must consult van Rynberk's recent exhaustive and illuminating summary of the problem. In broad outline van Rynberk's experiments are in general agreement with Bolk's scheme of localization, but there are certain discrepancies between the results of these two authors. Experimental evidence obtained by other authors, notably Rothmann, André-Thomas, Durupt, ten Kate, Simonelli, Rossi, and others, who adhere to the general concept of localization of function in the cerebellum, have obtained divergent results in respect of the specific regions of localization. Many are inclined, as did Bolk, to place the centre for movements of the eyes and jaw muscles in the anterior lobe, but Rossi and Ingvar were unable to agree to this and believe on the contrary,—as Ferrier (see *302*) had originally contended in 1876,—that the anterior lobe is associated with the coördination of that portion of the body musculature which prevents the animal from falling forward; while the posterior lobe is similarly looked upon as associated with the group of muscles which prevents the animal from falling backward, and Ingvar presents convincing experiments in which localized lesions occurred in the posterior and anterior lobes respectively in which the animal tended to fall forward or backward as the case may be. These experiments were substantially confirmed by Simonelli (*946*, *947*), though he placed upon them a somewhat different interpretation. Thus, Simonelli has described one result as follows: "After ablation of the posterior lobe there are to be seen dynamic phenomena, chiefly of an accessory type. They are characterized by dorsal extension of the head, extension of the anterior extremities, opisthotonus, falling backwards, and cries of motor agitation." It was pointed out also that only when the uvulus and nodulus were removed did falling backward appear.

This represents a brief, and I fear altogether inadequate, description of the type of evidence which has been adduced in the course of this difficult and interesting controversy. It would carry us far beyond the limits imposed by a single chapter to examine the experimental facts in greater detail, especially those recently brought forward by van Rynberk. For these the reader must consult the original descriptions.

DISCUSSION AND CONCLUSIONS

Let us now attempt to evaluate the evidence and try, if we can, to see in what direction it leads us in our attempt to establish the probable function of this obscure organ. The intermediate position taken by Rossi (*824*), namely, that in certain regions of the cerebellum there is a "prevalence of

representation" of various portions of the body musculature, would appear to be the only conclusion which we are at present justified in drawing. The anterior lobe of the cerebellum does evidently have more to do with the head than with other regions of the body, though when this lobe is removed or involved as in the case of Gordon Holmes' gunshot injuries, symptoms also appear in other portions of the body. The lobulus simplex appears to have a predelection for the neck muscles. Similarly, the anterior portions of the median lobe ("crus I"), when extirpated, lead to more pronounced symptoms in the fore limb than in the hind. When the posterior lobe is extirpated the animal tends to fall backwards rather than forwards, but symptoms nevertheless appear in all parts of the body. Clearly, therefore, we have no such well marked representation as in the case of the cerebral cortex, but even in the case of this latter organ it is arguable that the localization observed in the motor area is more or less an accident because it happens that the pyramidal tracts commence in that region. The function of controlling any given member is a complex result of the interaction of many parts of the brain,—of the organ as a whole,—and the motor area is merely a terminal nodal point along which this highly integrated influence finally travels. The old idea of centres for various specific functions has, in the case of the cerebrum, been effectually overthrown, and arguments of cerebellar function based upon comparisons with cerebral "centres" are built upon false premises. If it happened in the case of the cerebellum that direct fibre tracts in connection with the anterior horn cells commenced on the surface of the cortex, localized responses might be obtained when such a region was stimulated; but the cerebellar cortex has been evolved to meet the needs of the body musculature as a whole, and while it may be that certain portions of this organ have represented within them localized portions of the musculature, this is probably to be regarded as purely incidental to its more unitary function of regulating the delicately adjusted movements of the entire body.

Many writers, including Ingvar, have believed that the cerebellum is an organ of *equilibrium*. Perhaps the most suggestive evidence in favour of their views is the intimate association phylogenetically between the vestibular nuclei and the cerebellum itself. These authors stress the tendency observed clinically for falling to one side or the other in cases of cerebellar lesions. They also draw attention to frequent symptoms of vertigo. It does not follow, however, from this evidence that the cerebellum is an organ of equilibrium, nor is it always clear that the vestibular nuclei are uninvolved in clinical lesions. That it facilitates and adjusts certain equilibritory reflexes cannot be doubled,

but the fact remains that in complete absence of the cerebellum, though there is extensive motor incoördination, the animal nevertheless has no difficulty in perceiving the upright position (as judged by the presence of the righting reflexes). His difficulty comes when attempts are made to react in the normal way to these righting reflexes. This may appear to be an academic distinction, but it is of importance for comprehending the function of the cerebellum. One may recall also that the tonic labyrinthine reflexes are more easily elicited in the absence of the cerebellum than in its presence (Magnus), just as other tonic reflexes (*e.g.*, the stretch reflex responsible for the maintenance of decerebrate rigidity) have greater freedom when released from its restraining influence.

If the cerebellum is not an organ of equilibrium, it is accordingly proper to ask ourselves as to the precise nature of the regulatory influence which it exerts. The fact which is most outstanding is that the cerebellum receives afferent fibres probably from every skeletal muscle in the body. When the cerebellum is removed, delicately adjusted movements are forever made impossible. The power of voluntary contraction remains, but movements commence abruptly and continue beyond their allotted time. The cerebellum in other words, is an organ which facilitates accurate and delicate adjustment of complex movements, *i.e.*, synergia. Synergia has been defined as the faculty by which more or less complex movements subserving a definite function are associated in the performance of special acts (Babinski *42, 43,* Miller and Weisenberg, *715*). In the absence of the cerebellum movements become dissociated and ataxic, *i.e.*, asynergic.

In considering the way in which synergia is made possible our attention is naturally directed to the inhibitory fibres which form so important a constituent of the efferent tracts. To understand how this inhibitory mechanism controls movement, we may recall to our mind the example mentioned in another chapter. In a preparation in which the cerebellum is excluded by a section below the red nucleus, it is possible to study the influence of inhibitory fibres arising within the muscle itself. If, for example, a crossed extensor reflex is recorded before and after cutting the posterior roots, we find certain characteristic differences. The development of tension in the undeafferented muscle is more gradual; the tension attained is less; and the curve of relaxation, though commencing sooner, lasts longer than after the sensory nerves of the muscle have been excluded. The more gradual ascent has been interpreted as due to the influence of inhibitory fibres stimulated by contraction; they serve to prevent rapid and dangerous tensile stress, while the more gradual relaxation is probably the result of the functional activity of the proprioceptive nerves which

lead to reflex contraction (shortening reaction). The end-effect of the interaction of the two varieties of influence is a more gradual and more delicately adjusted movement of the muscle under excitatory stimulation.

One may urge that the function of the cerebellum is in the nature of a "*modulating*" influence, securing just such delicate adjustments as we have seen in gross form in comparing the normal and deafferented responses of the knee extensor in responding to crossed stimulation. One may suggest, furthermore, that this delicacy of adjustment is obtained through simultaneous control, inhibitory and excitatory, of antagonistic muscles. We have seen that the plan of reciprocal activity of antagonists is one which has been laid down in the spinal cord,—for in the spinal animal reciprocal innervation is the rule. In the eye muscles reciprocal innervation obtains after decerebellation (de Kleyn, *550*). We know that voluntary effort can overcome reciprocal innervation and cause simultaneous contraction of antagonists. After removal of the cerebellum this failure of the reciprocal spinal mechanism during voluntary activity is particularly pronounced, and it may be concerned in the production of that form of rhythmic activity which clinicians call "intention tremor." In addition the cerebellum secures the harmonious coöperation of separate muscle groups. Such, then, in brief outline appear to be the outstanding functions of the cerebellum.

CHAPTER XXI

The Nature of Higher Control

Having discussed at length the mechanism of tonic contraction, reciprocal innervation, and the central inhibitory process by means of which reciprocal innervation is brought about, we may now consider how these isolated processes coalesce to secure orderly and coördinated movements of an intact animal. This will entail a consideration of the influence of the higher centres of the nervous system upon tonic reactions, and also a study of the way in which voluntary contraction is superimposed upon postural contraction.

Recent investigations on the evolutionary development of the central nervous system indicate that it is proper to visualize the elementary reflex arc in the purely conventional way illustrated in figure 200. A single receptive neurone conducts an impulse to a "central" region where it communicates with an "effector" motor neurone by means of a synaptic junction. When the receptor is stimulated the effector organ is thrown into activity through this simple reflex arc. For the demonstration of the validity of these conceptions in the lower metazoa, we are indebted largely to the fruitful investigations of G. H. Parker (*750*). In certain of the sea anemones he has observed conducting systems in which these relatively simple conditions obtain (*750*, p. 202). With the growth of the organism more complex adjusting pathways are required, and the central nervous system of higher animals gradually developed in response to this need (Parker).

There are ample grounds for regarding the knee-jerk of a spinal animal as brought about through reflex arcs of the same order of simplicity as those found in the lower forms of animal. The receptive neurone in this case is the so-called "stretch afferent," and the effector neurone is the anterior horn cell, the axon of which passes directly to the muscle fibre. The synaptic connections in the cord cannot be extensive in view of the extraordinarily brief latency of the knee-jerk (Chapter XIII). We know that certain levels of the central nervous system influence the myotatic responses in various ways, but—and this is the important point—the higher levels of the nervous system, when acting upon the spinal arcs involved in the knee-jerk, *do*

not materially alter the latency of that reflex.[1] One must consider therefore how the knee-jerk is modified from above without there being a concomitant alteration in its latency. The theory which has been advanced to account for this and more general aspects of reflex phenomena had its origin in the investigations of Bell.

In the works of Sir Charles Bell one finds, as Campbell Thomson (*978*) has noted, a foreshadowing of our modern conception of levels of function in the central nervous system. In referring to the higher levels he says: "These nerves, additional and superadded to the original (spinal) system, *do not destroy, but only obscure that system,* and accordingly, when we separate

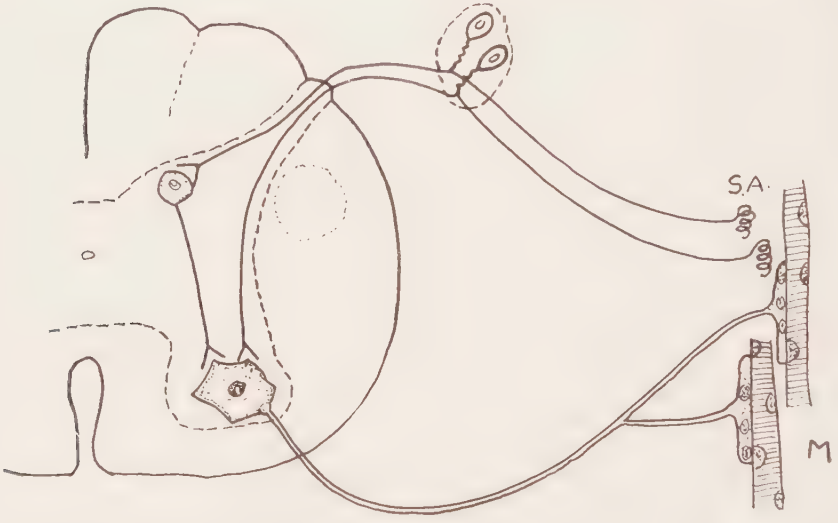

FIG. 200. A diagram of a simple spinal reflex arc. The knee-jerk is believed to involve reflex paths of this order of simplicity.

certain nerves, the original simple system is presented even in the human body." It was Hughlings Jackson (*516*), however, who first emphasized that destructive lesions in the higher centres yield "negative" conditions which permit "positive" signs (and symptoms) to emerge from the lower levels. This is the principle of "release," whereby the lower centres are "liberated" from higher control.

[1] The decerebrate jerk is actually somewhat less ($1–2\sigma$) in latency (*48*) than the spinal, whereas the opposite might have been expected if the impluse passed to the higher centres in the decerebrate animal.

THE IMPORTANCE OF RELEASE PHENOMENA IN THE PHYSIOLOGY OF THE NERVOUS SYSTEM

The conception of release phenomena which thus had its origin in the work of Sir Charles Bell (see *978*), has profoundly influenced our conceptions of nervous activity. The nature of this principle may be illustrated by taking as an example the signs and symptoms of hemiplegia. In this condition Hughlings Jackson argued that loss of voluntary power (negative condition) led to the appearance of positive signs. The signs consisted in a gross spastic condition which he looked upon as due to unrestrained activity of lower centres, not being caused, as was then supposed, by irritation incidental to the lesion. The significance of this generalization, though recognized by some especially in England, was greatly strengthened by Sherrington's discovery of decerebrate rigidity in 1896 (*882*). This gave experimental proof of Jackson's principle of release of function. Sherrington provided cogent reasons for believing that the characteristic postural rigidity which ensues in this condition is not due to irritation following upon the operation, for the condition persists indefinitely and it is not aggravated by subsequent section or mechanical irritation of the brain-stem. He attributed the result to the removal of inhibitory control normally exercised by the higher centres of the nervous system.

This fundamental conception has been further extended and elaborated and to great advantage by Henry Head. He (*448*, p. 185) points out that "the phenomena of disease are thought to be purely adventitious; they are spoken of as 'pathological,' and are supposed to bear no relation, even remotely, to any mode of response which has previously existed in the individual or the race. We believe, on the other hand, that in the gradual evolution of function the reactions of the lower centres have been changed to suit fresh conditions. The more complex an organism, and the more efficiently it responds with discrimination to external forces, the greater will be the need for such readjustment. Older modes of response must be modified or suppressed; some are utilized in the newly acquired complex act, whilst others, under normal conditions, are prevented from playing a part. But wherever diminution or removal of a dominant group of functions leads to an excessive outburst of energy, the more primitive responses have not been abolished; for had they disappeared completely in the process of evolution destruction of a higher centre would produce loss of function only, unaccompanied by signs of over-activity. Normally they are suppressed because they would disturb the more discriminative responses of higher centres; but they still remain capable of revival under conditions demanding urgent and impulsive action."

Head points out that the positive signs can develop either as a result of a strong stimulus, which causes the lower centres to break through higher control, or they may be due to lesions which destroy the higher centres themselves. This latter process he refers to as *disintegration*. Decere-

brate rigidity, therefore, is an example of disintegration. Other examples of this process may be cited.

That of *the mass reflex* is particularly important. When the spinal cord of man is divided and the period of spinal shock passes away, there follows a condition in which the slightest sensory stimulus may give rise to a very extensive response involving many of the spinal centres,—bladder and rectum, as well as those of the muscles of the extremities. This spreading of executant response has been termed by Riddoch (*807*) "the mass reflex," and is looked upon as being due to the absence of higher controlling centres which would normally restrict the afferent impulses in limited and well-defined channels.[2]

Another important contribution was made by Head (*448*) in his analysis of the "syndrome thalamique." It will be recalled that this organ is the "way station" for all incoming sensory impulses; from there pain impulses commence a fresh course, always culminating either in the cerebral cortex or in other regions of the thalamus itself. Loss of sensation resulting from lesions of this portion of the brain differs in no important way from that caused by direct interference with afferent impulses. But another important sign characterizes lesions of the optic thalamus, namely, the pronounced tendency "to react excessively to all potentially affective stimuli. The prick of a pin, painful pressure, excessive heat and cold, all produce more distress than on the normal side. At the same time pleasurable warmth may evoke an unusually vivid response and general affective states induce a more profound reaction over the disordered half of the body." (Head, *448*, p. 188). As Head points out, it was customary to attribute such pain and excessive responses to central irritation. The lesion was believed to initiate pain, and so to produce hyperalgesia, but this does not suffice to explain the clinical history of these cases. Haemorrhage with softening is the common cause of such symptoms, and this usually begins suddenly. The immediate result of it is ordinarily a depression of function; the hyperactive sensory phenomena are characteristic of the restorative periods which ensue later. There is thus not only loss of function but overaction, and Head has attributed this to the removal of the restraining influence of the cerebral cortex,—"disintegration with release of function and not irritation is the cause of thalamic overaction."

Head goes on to show that these examples of overaction, in which he includes decerebrate rigidity, show certain primitive characteristics. "They are not," he says, "fortuitous perversions of a normal function, as

[2] Dr. Viets has drawn my attention to a description of the mass reflex in 1870 by Parrot in L'Union Médicale, tom. 9, p. 137 (3rd ser.).

some have contended, but reveal to a certain degree the mode of action of the lower centres before they were dominated from above. The reaction is massive and exceeds any normal response. . . . . It is stereotyped, predetermined, and the same manifestations can be evoked from an abnormally wide receptive field" (*448*, p. 195). There is also less tendency to discriminate between different qualities of sensation. Stimulation of a touch corpuscle may produce substantially the same reflex response as a warm or cold stimulus or the stimulation of a "pain" ending. In the normal animal these diverse qualities of sensation are integrated and directed into appropriate channels. It is therefore fitting to ask ourselves as to the intimate nature of this integration.

How is it that afferent stimuli in the presence of the higher centres are prevented from radiating, as in the mass reflex, throughout the spinal cord? How are they directed to the higher reflex centres such as the cortex and thalamus, instead of traversing the phylogenetically older paths which they follow when the higher centres are removed? This is the problem which must be solved if we are to understand the nature of the control exerted by the higher centres of the nervous system in the adjustment of movement and posture.

Now the central nervous system is so integrated that influence from all levels is concentrated upon one structural unit, namely the anterior horn cell. The anterior horn cells taken as a group constitute the "final common path," and to this we may now give our attention.

THE FINAL COMMON PATH

The basis of modern knowledge of neuro-muscular coördination lies in the conception of the "final common path" (*903*, *904*, *910*). On the afferent side of every reflex arc is a receptive neurone which is reserved exclusively for impulses originating at a single receptive source (*e.g.*, a nerve ending at the base of a hair follicle). The central motor neurone which receives this afferent impulse also receives impulses from many other sources. This neurone may be likened to a funnel which gathers into one central path contributions from a large surface area. "It is the sole path which all impulses, no matter whence they come, must travel if they are to act on the muscle fibres to which it leads. Therefore, while the receptive neurone forms a *private path* exclusively serving impulses of one sort only, the final or efferent neurone is, so to say, a *public path* common to impulses arising at any or many sources of reception" (*910*, p. 116). In other words, "reflexes originated at different distant points, and passing through paths widely separate in the brain, converge to the same motor

mechanism (final common path) and act harmoniously upon it. Reflex arcs from widely different parts conjoin and pour their influence harmoniously into the same muscle. The motor neurones of a muscle of the knee are the *terminus ad quem* of reflex arcs arising in receptors not only of its own foot, but from the crossed forefoot and pinna, and tail, also undoubtedly from the otic labyrinth, olfactory organs, and eyes. Thus, if we take as a

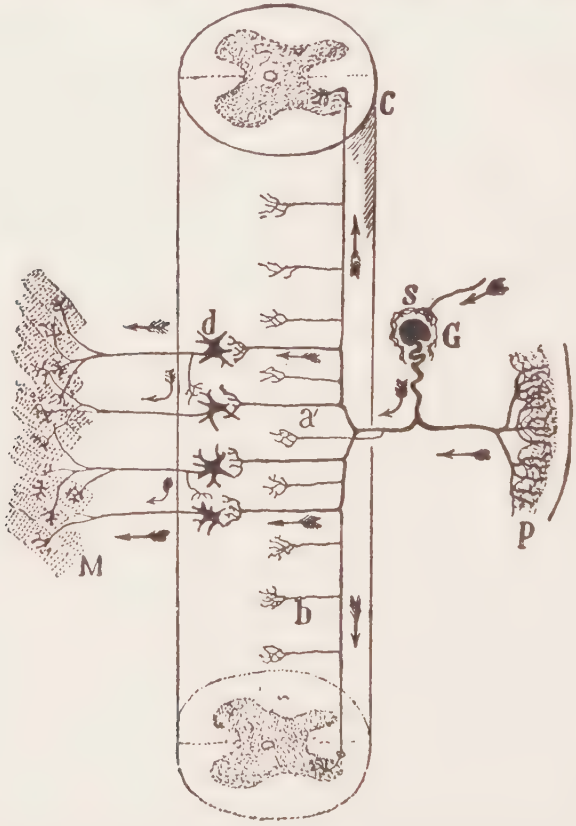

FIG. 201. A diagram from Ramon y Cajal showing the spreading and *convergence* of centripetal (sensory) fibres upon the anterior horn cells, thus illustrating the principle of the "final common path." (Ramon y Cajal, *789*, p. 531, 1909.)

standpoint any motor nerve to a muscle it consists of a number of motor neurones which are more or less bound into a unit mechanism; among the reflex actions of the organism a number can all be brought together as a group, because they all in their course converge together upon this motor

mechanism, this final common path, activate it, and are in harmonious mutual relation with regard to it."

The anatomical basis for the principle of the final common path, implying

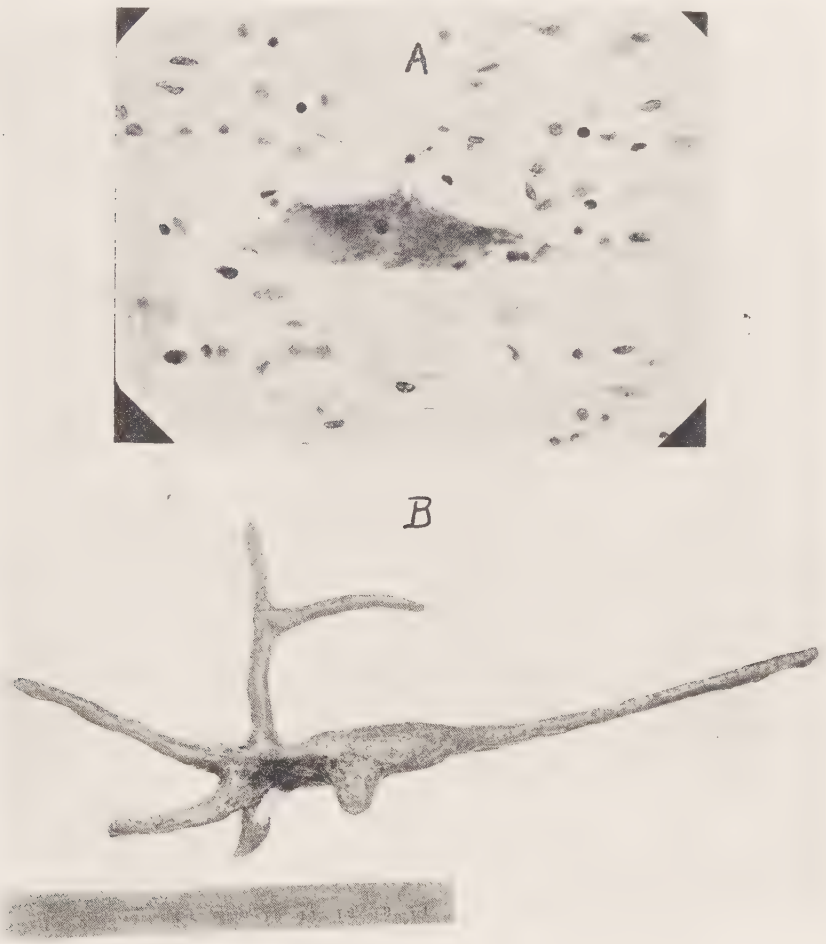

FIG. 202. A. One of Lhermitte and Kraus's (*635*) microscopic sections of the anterior horn cells of human beings (supplied by courtesy of Dr. Kraus).

B. A reconstruction of the anterior horn cell to show the great extent of its surface.

as it does *convergence* of a large number of impulses upon a common focal point, is provided, as Sherrington has pointed out, by the histological investigations of Cajal (*789;* see fig. 201). The recent observations of

Lhermitte and Kraus (*635*) on the morphology of the anterior horn cell lends added evidence favouring Ramon y Cajal's original findings. They have observed that the average anterior horn cell of human beings is 120 to 200μ in length, thus offering an extensive surface for a large number of synaptic junctions (see also Cajal's illustration of the branching connections of an anterior horn cell reproduced in figure 144, Chapter XVI). The length of the anterior horn cell is nearly five times its breadth (fig. 202 A), as shown in the model.

THE NATURE OF THE CONTROL EXERTED OVER THE FINAL COMMON PATH BY THE HIGHER CENTRES OF THE NERVOUS SYSTEM

The belief that one part of the nervous system may suppress activity in another dates from antiquity. Thus, in the *Aphorisms of Hippocrates* (Bk. 2, sec. ii, par. 46) one finds "Cum duo dolores simul minime eundem locum occupant, vehementior alterum obscurat."

This observation was also recognized by Galen, but it was Marshall Hall (*430*, 1838) who first noted (frogs) that removal of the hemispheres augments spinal reactions. Eight years later (1846) E. H. Weber (*1033*), after participating in the discovery of the inhibitory action of the vagus, suggested that the increased activity of the cord witnessed after removal of the brain is due to the severance of nerves which specifically inhibit the spinal mechanism. This doctrine was largely ignored, however, until the publication of Setschenow's thesis (*857*) in 1863. He found that stimulation of the corpora quadrigemina of the mid-brain (frog) increases reflex-time, as determined by the speed of withdrawal of the foot from acidulated water. Setschenow, on the basis of these experiments, was led to postulate the existence of an inhibitory centre in the mid-brain. Later (1865), however, Simonoff (*949*) found other points in the brain from which similar inhibitions could be elicited, and a number of other authors (see *895*) noted that inhibition could be obtained from stimulation of the cord itself. In 1863 Goltz (*404*) had made his well-known observation that mechanical stimulation of the frog's abdomen inhibited the heart. Schiff (*852*) and Herzen (*467*), on the basis of these and similar observations, promulgated the doctrine that all headward segments of the nervous system can and do exert an inhibitory influence on all segments lying further backwards. In keeping with these observations, Gergens (*393*) found that unilateral lesions of the cerebral cortex caused an augmentation of spinal reflexes on the contralateral side, and Simonoff (*949*) observed that stimulation of the cortex may restrain certain spinal reflexes. So striking at first did these observations seem that some authors (*e.g.*, Marie and Marinesco, see *895*) came to regard the pyramidal tracts as entirely inhibitory paths. The subsequent observations of Sherrington on stimulation of the cortex (*910*, p. 283), internal capsule (*910*, p. 284), and the pyramidal tracts in the spinal cord (*920*) made it probable that while inhibitory effects often predominate during such stimulation, excitatory fibres are nevertheless commingled with inhibitory fibres in the pyramidal tracts, the excitatory areas being often sharply localized in the cortex and internal capsule. The great enhancement of the scratch reflex which Sherrington observed (*908*) following spinal transection, is also clearly in keeping with the views of the early observers concerning the normal inhibitory

activity of the higher centres. More recently Sherrington and Sowton (*943, 944*) have found that the flexor reflex is immediately enhanced on section of the cord, and Forbes, Cobb and Cattell (*329*) found that the same is true of the electrical response. This enhancement of the flexor reflex is therefore in the nature of a release phenomenon (*892, 895*). In this connection it is of interest to recall that the cerebral ganglia of invertebrates often give rise to similar restraint. Thus, when a crawling worm is divided, the anterior

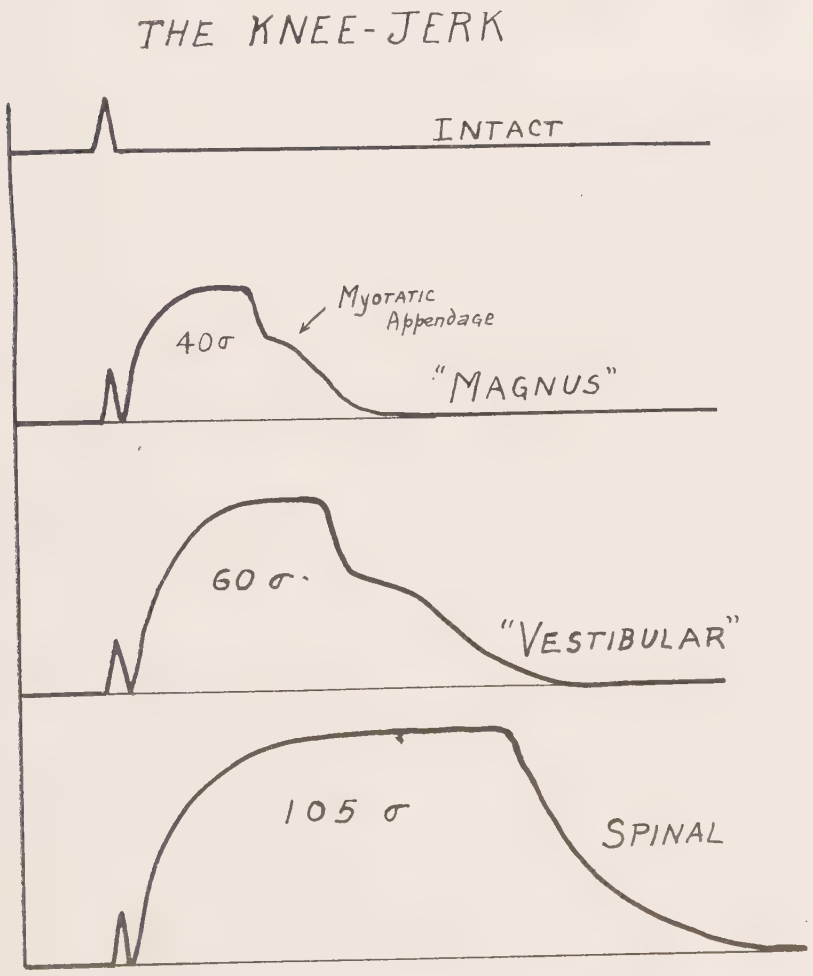

FIG. 203. The knee-jerk at various functional levels.
A. Normal animal (man), illustrating that it may be inhibited by "voluntary" activity.
B. Magnus preparation, single twitch.
C. Vestibular preparation, two volleys.
D. Spinal preparation, five volleys.

portion crawls serenely on while the posterior end writhes as a result of release from higher inhibition. Similarly the cephalopod *Eledone* on "decerebration" becomes increasingly active (see *895*). Similar observations have been made upon *Limulus* and *Astacus*. The extreme restlessness of Goltz's (*405*) (and more recently Pavlov's) decorticated dogs may also be recalled. For further discussion of these and similar observations, see *895*, pp. 837–841.

When considered broadly, the outstanding feature of the central nervous system is the progressive phylogenetic dominance of the cerebrum (*405*, *866*, *910*). When this "organ" is removed, though coördinated locomotor activities are still possible, the power of "voluntary" inhibition of these activities is lost, and with this is lost also the power of "voluntary" excitation of them. It may be taken, therefore, as an adequate generalization that the full dominance of the highest levels of the brain is made possible through power to excite and to inhibit activity of lower centres. When the powers of inhibition are abolished by removal of the higher centres, the general consequences are familiar to us in such release manifestations as spastic paralysis, etc. But, if we grant the principles of release of function and of the final common path as essential to the interpretation of the phenomena of reflex physiology, how are we to interpret the differences between the decerebrate and the spinal condition?

It is generally agreed that, as one sections the brain-stem at successive levels, the extent of functional release, as evidenced by the tonic coördination of the muscles, increases progressively until the level of section excludes the vestibular nuclei, when a condition of *hypo*tonicity supervenes. The occurrence of atonia in spinal animals might on casual reflection appear to be out of harmony with the conception of release phenomena. However, if we recall the variations of the most simple spinal reflex with which we are familiar, namely, the knee-jerk, as the brain stem is sectioned at successive levels, we obtain a more harmonious picture. Moreover, since the knee-jerk involves the neurones of the final common path, which are themselves directly subject to the influence of the higher centres of the nervous system, it serves as a delicate index of the condition of the final common path with reference to higher control.

An appended diagram (fig. 203) serves to illustrate the important features of the knee-jerk in the intact animal, and in the Magnus, the decerebrate, and the spinal conditions, respectively. In the intact animal, it is often possible, by "voluntary" effort, to produce complete inhibition of the knee-jerk (Bowditch and Warren, *141*).[3] This is indicated schematically by a

[3] The power of "voluntary" inhibition of the knee-jerk varies greatly among different individuals. By contraction of the flexor muscles it is, of course, possible to conceal a genuine extensor response, but one cannot conceal an electrical response of the knee-jerk,

tap stimulus not followed by a response. In the Magnus animal, on the other hand, or in an animal whose brain-stem is sectioned above the red nucleus, the knee-jerk is generally a single volley of impulses, *i.e.*, 40σ in duration, and the number of units responding for a given tap stimulus appears to be less in the Magnus preparation than in a red nucleus animal. In the vestibular animal, the knee-jerk tends to be a tetanus made up of two volleys.[4] Finally, in the spinal animal, the knee-jerk is of much more ample duration, being a tetanus of 4 to 8 volleys. This would appear to demonstrate in an unequivocal manner that the anterior horn cells do become progressively released from inhibitory control as the brain-stem is sectioned at lower and lower levels.

Now, we have reason to believe that the knee-jerk is a fractional manifestation of the generalized myotatic reflex responsible for the maintenance of decerebrate rigidity. We must therefore ask ourselves this question: "How is it, if, in the spinal animal, the final common path is more released than in the decerebrate, that decerebrate rigidity exists in the former and not in the latter condition?" A satisfactory answer to this question has not yet been offered. There is at hand, however, experimental evidence bearing on the question, and if a suggestion is not out of place, I would urge that the following factors will probably be found essential in accounting for this somewhat paradoxical situation.

In Chapter XVII evidence was presented indicating that in any reflex response of an undeafferented muscle the active contractile tension serves to stimulate proprioceptive inhibitors which modify the course of the reflex contraction, and that coördinated movement is in reality the summated result of a constant interplay of excitatory and inhibitory proprioceptor influence. If it happened that the local inhibitory pathways in the cord should, by any circumstance, be made increasingly direct, or that inhibitory impulses arising autogenously in the contracting muscle should be made increasingly effective, then the power of maintaining the myotatic reflex would be seriously impaired. Experimental evidence of this was obtained in the analysis of the stretch reflex. If the muscle under examination had been exposed in the course of an experiment, the resulting inflammation led

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and Hoffmann (493) has shown it can be made to undergo large variations by "voluntary" effort. The well-known fact that diverting the attention leads to an augmentation of the knee-jerk response points in the same direction.

[4] The statements regarding the knee-jerks in the Magnus and vestibular animals respectively are based upon observations from different preparations. More satisfying for this particular point will be observations drawn from the same preparation, but the desired evidence is not yet available. The point is now under observation.

more readily to stimulation of nociceptive inhibitory endings with the result that the plateau of a stretch reflex tended rapidly to diminish (lengthening reaction).

When, on the other hand, a decerebrate preparation is made spinal, a somewhat different condition supervenes, namely, a given inhibitory stimulus becomes *more effective* with reference to the neurones of the final common path. We have direct experimental evidence of this in the increased susceptibility of the knee-jerk to inhibition, and similar evidence has been obtained by Liddell and Sherrington (638) in their comparison of the spinal and decerebrate crossed extensor reflex. In the decerebrate animal the condition of depression following upon a single ipsilateral break-shock stimulus lasts for but a fraction of a second. In the spinal condition, on the other hand, the depression produced by a similar stimulus may last for several seconds. This has led to the suggestion that the *inhibitory* pathways become extensively "released" after exclusion of the vestibular nuclei, with the result that active myotatic contraction cannot be maintained in a muscle owing to the increased effectiveness of autogenous inhibition. If one inquire into the intimate mechanism by which such control over the inhibitory pathways is brought about, the following considerations suggest themselves as of importance.

We may first simplify our experimental conditions to the greatest possible extent. This has been done for us by Magnus and his collaborators. They have found that decerebrate rigidity continues to exist in a muscle of a vestibular preparation (*i.e.*, with brain-stem sectioned just above Deiter's nucleus) in which the proprioceptive labyrinthine influence has been excluded by section of both VIIIth nerves and in which the tonic neck reflexes are wiped out by section of cervicals I, II, and III on both sides (*679*, p. 434). One can add, furthermore, that the rigidity still exists in the quadriceps muscle of such a preparation after complete denervation of all muscles and skin of the opposite hind limb and of all other muscles and skin on the side examined. Now the maintenance of rigidity in a decerebrate preparation appears to be conditioned by one important factor, namely, the tension exerted upon the muscle in question by its normal anatomical attachments. Detach its tendon, let it shorten a few millimetres, and rigidity vanishes. Extend the tendon, and "rigidity" once more appears. In this relatively simple experiment we see at first hand what is undoubtedly the underlying reflex mechanism necessary for the maintenance of postural tonus.

Since the presence of the vestibular nuclei is necessary for the continuance of well marked myotatic reflexes (Magnus, *679*), this centre must exert a constant influence on the local inhibitory pathways, such that the neurones

of the final common path are relatively inaccessible to inhibitory impulses. Unfortunately, we do not know the precise mode of termination in the cord of fibres of the vestibulo-spinal tract; this information might give us a clue to the solution of the physiological mechanism involved. If one were to postulate a mechanism which would be in keeping with well-recognized morphological conceptions, it would be necessary only to assume the existence of an internuncial neurone between the incoming inhibitory fibre of the posterior root and the ventral horn cell. If this interuncial neurone were continuously inhibited from above, this would block the path across the cord, or at least make it difficult to traverse (fig. 204). In view of the extensive bifurcation of the incoming posterior root fibres (*789*, *846*), the end-result of operation of such a mechanism would be that while the local reflex path across the cord would become obliterated, the ascending paths to the mid-brain would remain functional, and in this way incoming sensory impulses would be deflected up the cord for higher integration.

LONG-CIRCUITING

This process of deflection of impulses up the cord to the higher centres may for convenience of reference be designated "long-circuiting." In the decerebrate animal it is evident that centripetal impulses arising locally (*e.g.*, in the muscle) often influence the centres of the spinal cord *indirectly*, through the higher levels of the nervous system. An example of such indirect influence was given in Chapter XIII in describing the inhibition of the knee-jerk. It was observed that the first knee-jerk after an inhibitory stimulus is often less affected than the second or third (see fig. 109). This suggested that whereas the local inhibitory pathways exerting a *direct* control upon the anterior horn cells of the cord were in these instances few, the number of pathways which exerted this control by means of the higher centres was large.

It is obvious that the process of long-circuiting of impulses up the cord is of fundamental importance for the integrative processes occurring in the higher centres. It would appear, moreover, that so long as a given controlling higher centre is present the majority of afferent impulses are long-circuited in this way. When, however, the higher centres are cut away, the majority of impulses pursue the phylogenetically older paths across the cord. There are many other examples of this variety of long-circuiting, and one recorded by Amsler (*25*) is particularly instructive. He found in lightly anaesthetized animals that stimulation of the central end of the sciatic nerve caused: (1) the well-known rise of blood pressure; (2) inhibition of the heart; and (3) a reflex "cry." As anaesthesia became

deepened, the loudness of the cry and the extent of the cardiac inhibition diminished *pari passu* and became extinguished together. He inferred from this that the cry on the one hand and the inhibition of the heart on the other, were produced reflexly through stimulation of pain fibres. He then found that if morphine were used as an anaesthetic, the same sequence of events occur as he observed with increasing depths of ether anaesthesia. When a certain depth of anaesthesia (morphine) had been attained, no matter how strongly the sciatic nerve was stimulated no inhibition of the heart occurred and no audible cry could be evoked. When, however, the superficial layers of the cerebral cortex were removed, even though the animal were under deep morphine anaesthesia, the cry and cardiac inhibition immediately returned. Amsler concluded from these observations that so long as the cerebral cortex remained intact the pain impulses were long-circuited through this region (in this way incidentally reaching the higher integrative fields of the cortex). When these higher centres were removed, the nociceptive impulses then immediately traversed the phylogenetically older reflex paths through the thalamus. After the cerebral cortex had been removed, no matter what the dose of morphine given might be, the reflex path through the thalamus remained unaffected. These experiments illustrate in a very striking way the importance of long-curcuiting of sensory impulses in the brain-stem. In the case of "pain" fibres, it is of the utmost importance for the welfare of the organism that the impulses which they convey should reach the higher integrative levels of the cerebrum.

There is little available information as to the way in which this long-circuiting is brought about, but the general scheme suggested below in figure 204 may prove worthy of consideration. It rests upon the assumption that the anterior horn cells of the spinal cord are, as it were, "protected" from the sensory fibres entering the posterior root by one or more internuncial neurones. If one of these internuncial neurones is *constantly inhibited*, the path of conduction in the cord from posterior root to anterior horn cell will be permanently interfered with, and by appropriate cell connections the impulses entering the posterior horn can be conceived of as always progressing up the cord so long as the inhibition continues, but immediately the inhibitory influence upon these internuncial neurones is taken away, as by severing the spinal cord, it will then be possible for the impulses to pass once more by these older conduction paths. Such a scheme cannot in the present state of knowledge be elaborated in detail, but it provides a tangible picture of the way in which the cells of the spinal cord (to take this specific instance) are "protected" in the decerebrate condition from inhibitory impulses arising in the limb itself, and very little elaboration

is required to make the schemata meet the more varied phenomena presented by the "mass reflex" discussed above.

Such a scheme is well in keeping with the important morphological fact discovered by Sharpey-Schafer (*864*) and since corroborated by Collier and Buzzard (*207*), Kappers (*539*) and others (see *464*, p. 344), that the pyramidal *tracts do not all terminate around the anterior horn cells* for large numbers end upon internuncial neurones. Some cortico-spinal fibres, as

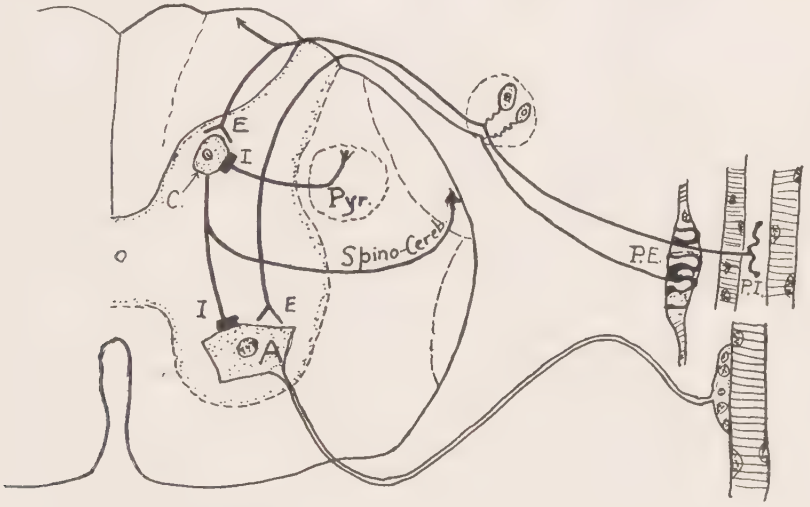


FIG. 204 A. A scheme of synaptic connections in a segment of the spinal cord, designed to illustrate one aspect of cortical control over the local proprioceptive inhibitory pathways. Two proprioceptive afferents are introduced into the figure (P.E. and P.I.). The proprioceptive excitor, or "stretch afferent," passes directly to the anterior horn cell. The proprioceptive inhibitor passes to an internuncial neurone (*e.g.*, Golgi "Type II"). About this neurone there also terminates a fibre from the pyramidal tract, activity of which causes inhibition of the internunical neurone. When the path to the anterior horn cell, A, is blocked through activity of the pyramidal fibre, the impulses set up by P.I. can then only pass up the cord in the posterior column. This represents in simplest form the underlying mechanism which would account for "long-circuiting." For abbreviations, see figure 204 B.

Sherrington and co-workers (*421*, *633*, pp. 208 and 220) demonstrated by a modified Weigert-Pal method do pass directly to the cells of the anterior horn.

Convincing experimental evidence of the intimacy of connection between the pyramidal tracts and the neurones of the final common path has recently been given by Cooper and Denny-Brown (*211a*), who find that when the

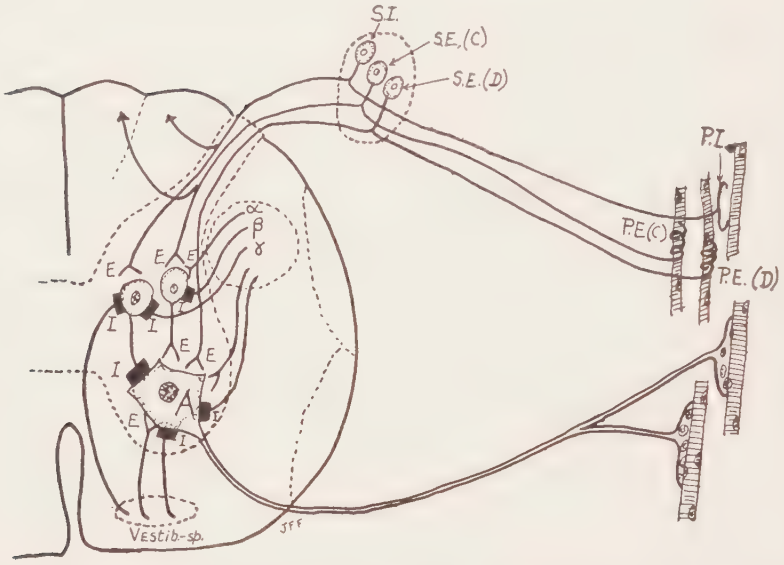


FIG. 204 B. A scheme similar to that shown in figure 204 A, but in which have been introduced a sufficient number of synaptic connections to deal more completely with the phenomena exhibited in the interaction between cortical and proprioceptive control of the final common path. The reader may consult the text for a detailed description of the consequences of activity of any one of the elements indicated.

E., an axon termination which, when in activity causes excitation of a contiguous neurone.

I., an axon termination which, when in activity, causes inhibition of a contiguous neurone.

P.E.(C), a proprioceptive end-organ of unspecified morphological characteristics which, when activated by an adequate stimulus, leads mediately to excitation of the anterior horn cell through activation of an internuncial neurone.

P.E.(D), a similar proprioceptive excitatory end-organ which, on activity, leads to direct excitation of A. These two proprioceptive excitatory end-organs have been referred to in the text as "stretch afferents."

P.I., a proprioceptive end-organ different from P.E. but of unspecified morphological characteristics which, on activation, leads mediately to reflex inhibition of a unit of the final common path through stimulation of an internuncial inhibitory neurone.

S.I., *S.E.(C)*, *S.E.(D)*, indicate the posterior root ganglion cells corresponding respectively to P.I., P.E.(C) and P.E.(D).

Pyr., pyramidal tract.

α, β, and γ, indicate cortico-spinal fibres which terminate variously in excitatory and inhibitory endings around internuncial neurones.

Vestib.-sp., the vestibulo-spinal tract.

Spino-Cereb., fibres passing to the direct spino-cerebellar tract.

A, an anterior horn cell of the final common path.

M, skeletal muscle fibre.

motor area of the cortex (monkey) is stimulated at a known rate, mechanical and electrical waves of the same frequency are observable in both flexor and extensor muscles.

Our scheme also has the advantage of harmonizing with Hoffmann's conception of voluntary activity discussed in Chapter XIX. In figure 204 B several elementary possibilities of pyramidal control are dealt with graphically. Three cortico-spinal fibres, α, β, and γ, are represented as embouching respectively: (1) in an "excitatory" ending upon an internuncial neurone *excitatory* to the anterior horn cell, *A;* (2) in an "inhibitory" ending upon the same neurone; and (3) in an "inhibitory" ending upon another neurone *inhibitory* to the anterior horn cell, *A*. Other cortico-spinal fibres end directly upon the cells of the anterior horn, but these do not immediately concern our theme.

α. Activity of pyramidal fibre, α, will lead to excitation of the anterior horn cell, *A*, and this excitatory effect will become summated in the cord with excitatory impulses originating in the "stretch afferent" organ, *P.E.*(*C*).

β. Activity of pyramidal fibre, β, on the other hand, will lead to withdrawal of activity from the anterior horn cell and will in addition form an impediment to the passage of the excitatory impulses originating in *P.E.*(*C*). This represents one form of inhibitory control.

γ. Finally, activity of pyramidal fibre, γ, will lead to suppression of impulses arising in the nociceptive proprioceptor afferent, *P.I.* which causes inhibition of anterior horn, *A*. It is this form of inhibitory control which would result in the "protection" of the final common path from autogenous inhibition set up by contraction. This latter case is illustrated in the simplified diagram given in figure 204 A. As the vestibular nuclei appear to exert this type of "protective" inhibitory control over the final common path, fibres from the vestibulo-spinal tract have been introduced into figure 204 B, and are represented as embouching both on the internuncial neurone and directly upon the anterior horn cell. Fibres from the rubro-spinal, tecto-spinal, olivo-spinal, and intersegmento-spinal tracts are omitted to avoid confusion.

δ. A fourth, or δ pyramidal fibre, might have been introduced into figure 204 B for the sake of completeness. Activity of the fibre would have led to *excitation* of the internunical cell (on the left) which would in turn have led to active *inhibition* of *A*.

The four cases meet every possibility of cortical influence in the simple situation presented by the diagram. The treatment is therfore both necessary and adequate for dealing with the conditions postulated. This treatment provides, moreover, a relatively simple method for visualizing the

way in which reflex cortical control adds itself to the lower reflex proprioceptive control of muscle activity. To take a single example, simultaneous activity of pyramidal fibres, α and γ, will give rise to coöperative interaction between these fibres and the excitatory "stretch afferents," *P.E.*(*D*) and *P.E.*(*C*), leading to increased excitatory activity of *A* with consequent contraction of the muscle-fibre, *M*. Be it noted that activity of pyramidal fibre, γ, will cause suppression of the autogenous inhibition resulting from active contraction of *M*, and this in turn will assist in the *maintenance* of the contractile tension. It is evident that these postulations harmonize with Hoffmann's observation that the action currents of tendon reflexes become augmented during "voluntary" contraction, for according to our scheme, the greater the number of γ pyramidal fibres in activity the greater would be the number of A units capable of responding to excitatory impulses from *P.E.*(*C*) or *P.E.*(*D*). Or, conversely, Hoffmann's result could also be accounted for by mere withdrawal of activity from β pyramidal fibres. It would be in keeping with the known complexity of central nervous control to assume that both factors are at work.

Such a scheme of locomotor coördination has the logical advantage of calling upon few postulates. Thus, it requires only those assumptions found necessary in Chapter XIV to account for central excitation and inhibition. It conforms, moreover, with the all-or-none principle. Active tension of the skeletal muscle, whether it be from a direct myotatic reflex (*i.e.*, "muscle tonus;" Chapter XV) or whether it result from cortical activity (*e.g.*, of an α pyramidal fibre), is looked upon as due to the all-or-none type of response of individual fibres (see Chapter IV, on asynchronous multifibre summation). Indeed, there is no evidence that muscle ever develops or maintains tension in any other way (Chapter XVI).

The theory takes into account the "lengthening" and "shortening" reactions and the proprioceptive excitors and inhibitors by which these "reactions" are governed (Chapter XVII). Slight amplification of the scheme along the lines set forth in figure 184 (Chapter XVIII) will make it meet the case of reciprocal innervation. The conception deals moreover with the somewhat paradoxical differences between the spinal and the decerebrate condition, and offers an adequate basis for description of the phenomena observed in the "mass reflex." The symptoms and signs of spinal shock, if regarded as due to release of inhibitory pathways, though not as yet specifically dealt with, will undoubtedly find an adequate "explanation" along the lines set forth in figure 204. As already mentioned, the schema calls only upon well-established morphological conceptions, and it attaches especial significance to the fact, not sufficiently emphasized in neurological

literature, that the pyramidal tracts do not all terminate directly upon the neurones of the final common path, for many embouch upon the internuncial neurones. Finally, it gives a basis for comprehension of the harmonious coalescence,—so important to the coördination of movement,—of "voluntary" and "tonic" contraction.

It is with these points in mind that the conception is offered for the reader's consideration. Be it understood, however, that "the aim of such a provisional scheme can but be '*pour préciser les idées*,' so the further and the better to test them against fact."

SUMMARY

The present chapter does not readily lend itself to a brief summary since it attempts to correlate into a workable scheme all of the phenomena described in the previous chapters.

The principles of release of function and of the final common path are described, and are urged as essential to any treatment of the physiology of the nervous system.

The condition of the final common path with reference to excitation as the nervous system is sectioned at various levels is described. It is suggested that the important difference between the decerebrate and the spinal animal is caused by the release of the local inhibitory pathways.

Diagrams are given in figures 204 A and B illustrating the nature of a synaptic mechanism which will account for the coöperative interaction between cortical and tonic (*i.e.*, myotatic) contraction, and other important features of reflex physiology.

APPENDIX

"La science a devant elle deux obstacles qui entravent sa marche: c'est d'abord la défectuosité de nos sens pour découvrir les vérités, et puis l'insuffisance du langage pour exprimer et pour transmettre celles que nous avons acquises. L'objet des méthodes scientifiques est d'écarter ces obstacles; la *Méthode graphique* atteint mieux que toute autre ce double but. En effet, dans les recherches délicates, elle saisit des nuances qui échapperaient aux autres moyens d'observation; s'agit-il d'exposer la marche d'un phénomène, elle en traduit les phases avec une clarité que le langage ne possède pas."

—E. J. Marey, *La Méthode Graphique*, 1885, p. i.

APPENDIX

Apparatus and Methods

A. the myograph

As there is no adequate description of recent developments in the technique of myography, it may be useful if an account is given of the torsion-wire myograph and of other details of procedure employed in the course of the investigations upon which this monograph is based.

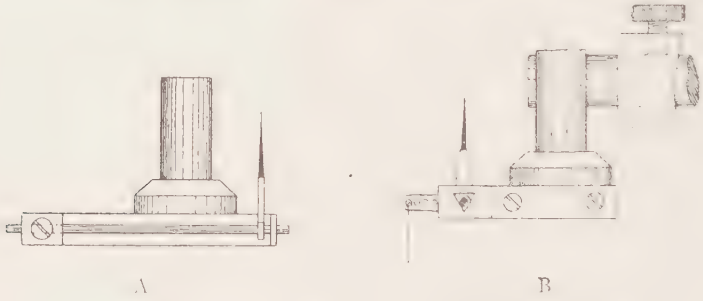
Successful measurement of such relatively brief intervals as the latent period and the period of rigidity of skeletal muscle requires a mechanical recording instrument of enhanced accuracy. Several myographs have been utilized but all were of the torsion-wire type devised by Sir Charles Sherrington (*990*). The precise details which I now give refer to the last and most successful instrument used in the course of the research (see *357*).

A piece of steel piano wire 45 to 50 mm. in length and 1.5 mm. in diameter is securely fixated at one end by being screwed into a perforated metal piece projecting from the metal body of the myograph (see fig. 1 A). The other end rests free in a V-shaped slot (fig. 1 B). Using a V-shaped slot ensures that torsion of the wire shall occur about its central axis. This prevents any distortion such as was found to occur if the free end of the wire rested on a knife edge. Soldered at right angles (horizontally) at this end of the torsion wire is a short slotted lever-arm (fig. 1 B) to which the muscle is attached, when pulling vertically. Another similar slotted arm is soldered in the same place vertically for attachment of the muscle when pulling horizontally (not shown in figure 1 B, but see photograph, figure 2). Fixed to the top of this vertical arm is a light steel needle 15 to 18 mm. in length. The end of the needle is ground (by hand) to a uniform diameter 0.06 mm. for a distance of 2 mm. When magnified 18 times as in these experiments, this point casts a shadow approximately 1 mm. in diameter on the photographic plate. The body of the myograph is equipped with a heavy metal collar (fig. 1 A) by which it is securely bolted to a rigid metal upright. A photograph of the myograph is shown in fig. 2.

Previous experience in the laboratory had made it evident that nothing short of a framework of heavy iron girders fixed in cement could provide a support for the myograph which was adequately rigid to prevent extraneous

vibration. The myograph was accordingly attached to a solid iron column 4.5 cm. in diameter fixed above and below into 10 cm. iron girders as shown in figure 5 and 6. The object of the V-shaped arms suspended from the upper transverse girder is to prevent lateral vibration. Each transverse girder was fixed at its outer end into the cement wall of the building. The inner end of the lower girder rests on a transverse foundation beam of the building as shown in figure 5. When fixed to this framework the myograph proved for the purposes in hand quite free of extraneous vibration.

The natural vibration frequency of such a myograph was found to be 1600 per second. A more recent instrument built in approximately the same way, but with a somewhat lighter needle, has a vibration rate of approximately 2000 per second. A record showing the natural vibration rate of the 1600 per second myograph is shown in figure 3. This was taken by



A B

FIG. 1. A, and B,—side and end views of the myograph (actual size). The fine point on the end of the myograph needle is not shown. Figure 1 B shows the V-shaped slot in which the free end of the torsion-wire rests. (*Quart. Journ. Exper. Physiol.*, vol. 15, p. 350, 1925.)

quickly cutting a thread which supported a weight suspended from the myograph arm. Time is indicated at the top of this figure in 0.02 seconds. In figure 4, a record is shown in which one of the earlier myographs was used. At the height of tetanus the ligature slipped in such a way as to set the whole system into vibration (460 per second). The limiting vibration frequency in this case proved to be that of the needle which cast the shadow, and not of the torsion-wire. By changing the dimensions of the former a higher natural frequency was obtained.

A natural frequency of 1600 complete vibrations per second ensures that the myograph is capable of following mechanical changes with no distortion provided the movements to be recorded are not quicker than the time required (0.3σ) for a full swing (*i.e.*, $\frac{1}{2}$ vibration) of the naturally vibrating

FIG. 2. A "close-up" photograph of the myograph showing its attachment to the iron frame-work. If examined with a lens the fine tip of the needle (0.06 mm.) can just be seen.

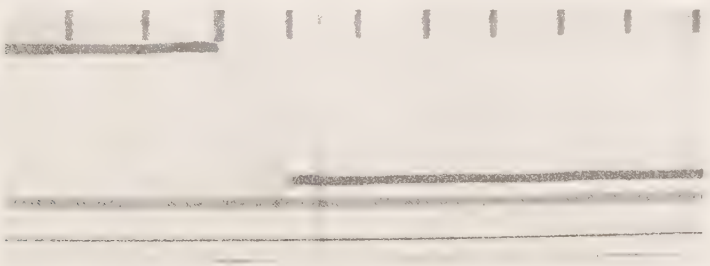


FIG. 3. A photograph showing the frequency of the naturally vibrating myograph. Time is indicated above in 0.02 second which shows the frequency to be approximately 1600 per second. The rapid decrement in the amplitude of the successive waves (indicating the extent of the damping) should be noted. (*Quart. Journ. Exper. Physiol.*, vol. 15, p. 352, 1925.)

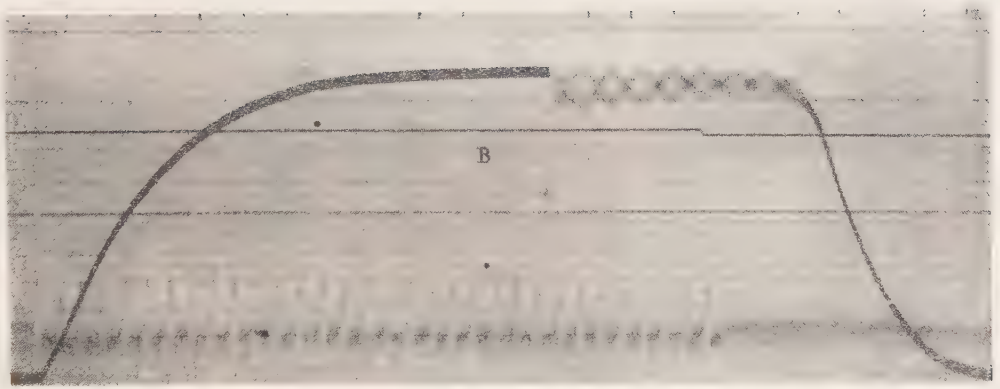


FIG. 4. Showing the vibratory characteristics of the myograph when attached to the muscle. At the height of the tetanus the ligature slipped very slightly and set the whole system into its own vibration frequency (460 per second). Time above = 0.04 second. (*Proc. Roy. Soc.*, vol. 97B, p. 421, 1925.)

myograph. With such an instrument, therefore, measurements may be made significantly to 0.3σ on the mechanical record. In the case of measurements of the period of latency this natural frequency ensures that the mechanical delay of the recording instrument owing to inertia is as low as 0.3σ and is probably much less. The latencies in certain of experiments recorded in this monograph have been measured to 0.1σ, but as the experimental error in analyzing the plates has been shown to be about 0.15σ, nothing is urged as significant beyond 0.2σ.

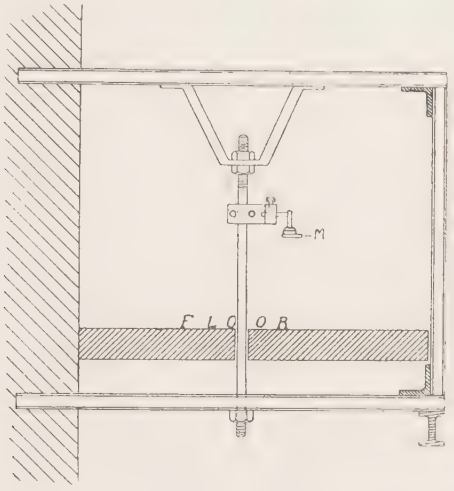


FIG. 5. A diagram of the iron frame-work used to support the myograph (M). The figure has been drawn on a scale of 1 to 35 as reproduced; the myograph, however, is somewhat out of scale, but its relative size may be seen in figure 6. The shaded area on the left is the brick wall of the building into which the ends of the girders are cemented. (*Quart. Journ. Exper. Physiol.*, vol. 15, p. 352, 1925.)

B. THE GALVANOMETER AND SIGNALS

The pointed needle of the myograph intercepted the beam of light (fig. 3) from a galvanometer (Einthoven-New Cambridge model). A silvered quartz string, 4μ in diameter, was used, which had a resistance of 2,000 ohms. It was ordinarily used at a tension of 7 to 8 mm. deflection per 1 m.v., or approximately 50 metres per ampere, according to the scale of string tensions introduced by Forbes and Ray (*333*, p. 439). A second string 2.5μ in diameter with a resistance of 3,500 ohms was used in later experiments. In prolonged experiments requiring continuous use of the galvanometer for 30 to 40 minutes, the radiation from the arc, though filtered through an alum bath, caused some tightening of the string owing to warming. This difficulty has been minimized by cutting down the arc and

by turning it and the field of the galvanometer off whenever they were not in use. Observations of the string tension were, therefore, taken immediately after and, if possible, in the midst of any given series of observations.

In early experiments two silver-chloride pin electrodes were used as leads, Zn-$ZnSO_4$-NaCl leads having been found wholly impracticable on account of movement of the proximal wick, but it was subsequently found for certain purposes more satisfactory to use a *combination* of the silver-chloride pin and the zinc-sulphate leads, the former being used proximally (inserted into the belly of the muscle through a "window" in the skin), the latter distally, the wick being fixed securely around the tendon by a bead. As this disposition of the electrodes is unusual, the advantages may be mentioned: (1) There is little or no polarization of the leads with time, as invariably occurs after 1 to 2 hours with two AgCl electrodes; (2) the injury, demarcation and electrode currents, whose combined magnitude is much the same from one preparation to the next, when balanced, remain so for a greater length of time than with other leads; (3) the electrodes move uniformly with the contracting muscle, even when great shortening is allowed, so that extraneous movements of the string due to shifting of the contact are avoided; (4) the responses can be made monophasic without tissue destruction by applying K_2HPO_4 (1.3 per cent) to the (distal) wick electrode. Potassium has usually been used in this way only in small amounts to cut down the diphasic excursion as monophasic responses were not desired; and, finally, (5) as breaking of the tendon during the tetanus is not uncommon, it is inadvisable to damage the tendon by inserting a silver lead. I have repeatedly observed, however, that if the tendon electrode is replaced by a silver electrode the action currents are more precise and appear to be considerably briefer. In fact a number of observations suggest that the smaller the area of the leading-off electrodes the more brief is the action current, even when completely monophasic.

The stimuli have been delivered to the nerve by a Sherrington torsion-wire separation key (*933*). The stimulating electrodes (silver wire) were 8 mm. apart on the nerve, kathode toward the muscle, and care was taken to minimize escape by keeping the electrodes at least 5 mm. distant from the surrounding tissues. Records were occasionally taken with submaximal stimuli and these show that the size of the electrical response varies directly, other things being equal, with the degree of plateau tension developed, *i.e.*, with the number of muscular units stimulated, which is in keeping with the results recently obtained by Watts (*1019*). An example of such a record is shown in figure 8.

The string of the galvanometer was brought to a focus in the same plane

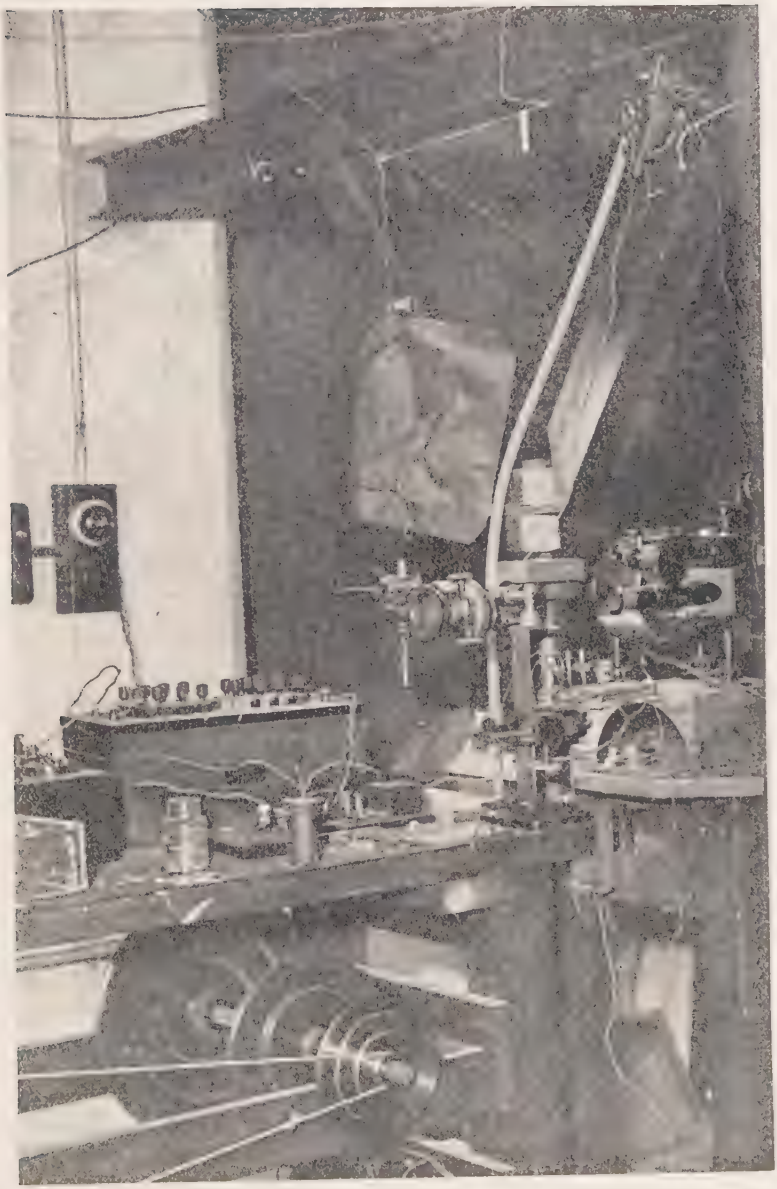


FIG. 6. A general photograph of the recording apparatus showing the iron girders which support the myograph. On the extreme right is the galvanometer, below and to the left of which is the cork floor of the moist chamber mounted on a rachet-and-pinion stand. The focussing lens is also seen. The camera was ten feet in front of the string of the galvanometer.

as the myograph needle and the two were then focussed by an ordinary lens on the camera. The latter was of the Cambridge oil (or water) plunging type, arranged with knock-down keys in the path of an arm attached to the moving plunger of the camera. These were connected with magnetic make and break keys (fig. 7) in front of the camera which had styles casting a shadow on the plate. By this method the *actual circuits used in stimulating* were signalled on the plate. Time was indicated in the usual way by a rotatory time marker in intervals of 20σ. The stimuli, when repetitive, were monophasic (break) induction shocks delivered by a torsion-wire separation key.

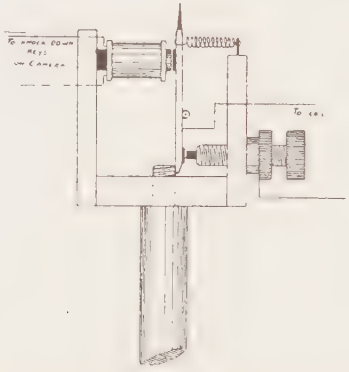


FIG. 7. A diagram of the optical signal by means of which the moment of stimulation was indicated on the photographic plate. Such a key may be used either as a make or a break key in the primary of an inductorium, or as a short-circuiting key across the terminals of the secondary. The small circle near the centre of the diagram indicates the pivot of the armature. (*Quart. Journ. Exper. Physiol.*, vol. 15, p. 353, 1925.)

C. THE PREPARATION OF THE INTACT MUSCLE OF A DECEREBRATE FROG FOR ISOMETRIC RECORDS OF CONTRACTION

To ensure the normality of response, it is of the utmost importance to maintain active circulation in the recording muscle, and this in turn depends upon the maintenance of a high blood-pressure and adequate respiration. The preparation (*Rana temporaria*) was decerebrated by quickly crushing the forepart of the skull with strong artery forceps, the forceps being allowed to remain on the skull until the following dissection was made. By this method, very little blood need be lost. A small slit was made beside the urostyle on the side intended for use and the lumbar nerve trunks withdrawn upon a small glass hook and severed, especial precautions being taken to prevent damage to the blood vessels. The sciatic nerve was then

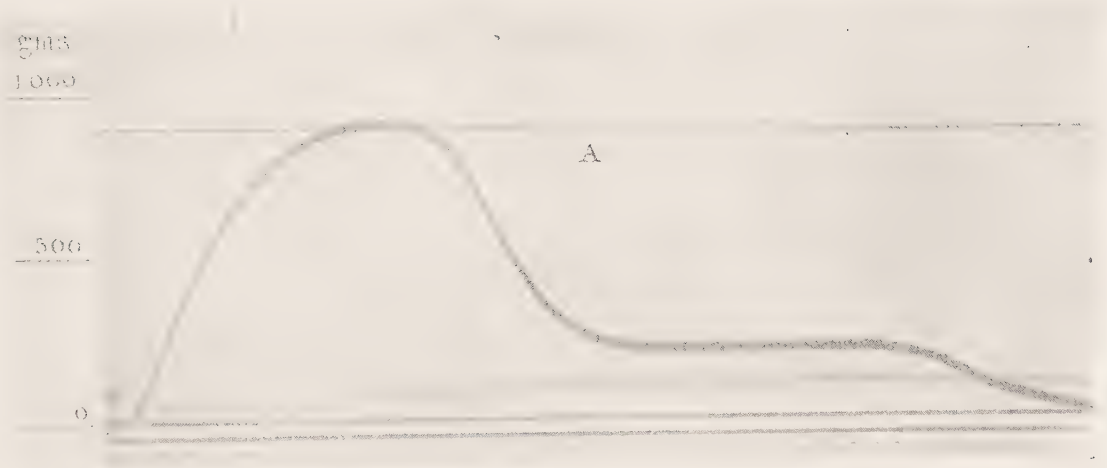


FIG. 8. Mechanical and electrical responses of gastrocnemius to sub-maximal stimuli which, just as the plateau was reached, fell to three-fourths to four-fifths of their original size owing to their being inadequate to stimulate all of the fibres. The electrical responses fall proportionally with the mechanical response. T = 16° (*353*).

reëxposed by a second incision in the thigh. A needle pressed at right angles through the knee joint into a special metal upright, shown in figure 10 served to fixate the recording muscle. This ensures that the muscle shall pull in its accustomed direction. To free the distal lead from all obstruction, the foot was cut off just above the ankle joint (after previously tying a ligature to prevent bleeding). The majority of the blood in the leg accordingly passes into the gastrocnemius muscle.

To prevent any alteration in the response caused by the muscular deterioration or oedema following upon the cutting of the nerve, the responses were taken immediately (5 to 10 minutes) after the completion of the dissection. No trials for threshold were taken as there was very little variation from one preparation to the next. Consequently the "condition" of the muscle was as fresh and as normal as was possible. When temperature alterations were being observed twelve to sixteen twitches were usually taken at the first temperature, and, after an interval of 1 to 2 hours a corresponding number were taken at the second temperature. If anything went wrong with the first two or three records, a new preparation was always found to be the most satisfactory expedient. Particularly was this true in the case of preparations of sartorius in which, owing to the difficulty in maintaining the circulation, responses sometimes ceased to be "normal" after two or three responses. Since there are special technical difficulties in recording simultaneously the mechanical and electrical responses of the intact sartorius stimulated through its nerve, some description is necessary of the method employed for it.

The preparation was decerebrated in the usual way, and the lumbar nerve trunks freed and severed as high as possible. The cut ends were ligated and freed distally as far as the lymph "heart," where, to secure a greater length they were sometimes pulled from beneath the anastomizing vessels. The nerve branches to the adductors were now cut in the thigh and as far as possible to the other thigh muscle were also severed. The sartorius was carefully exposed and freed along its outer margin and also along its inner margin to within about 2 mm. of the entry of the nerve. The knee was ligated and the leg cut off below the ligature, the thread ends of this ligature were used to tie the end of the femur to a metal upright in the moist chamber, the thigh being fixated to the cork floor of the moist chamber with pins, in such a way that the sartorius pulled in its accustomed direction.

The preparation was placed somewhat on its side in the moist chamber and Sherrington glass-shielded electrodes applied to the whole lumbar trunk. For sartorius, a less "stiff" myograph of the usual type was employed; by constructing it of a short length of light steel wire a frequency of 430 per

second was obtained. Silver or zinc-sulphate leads were used as in gastrocnemius, the wick of the zinc-sulphate lead being around the tendon and

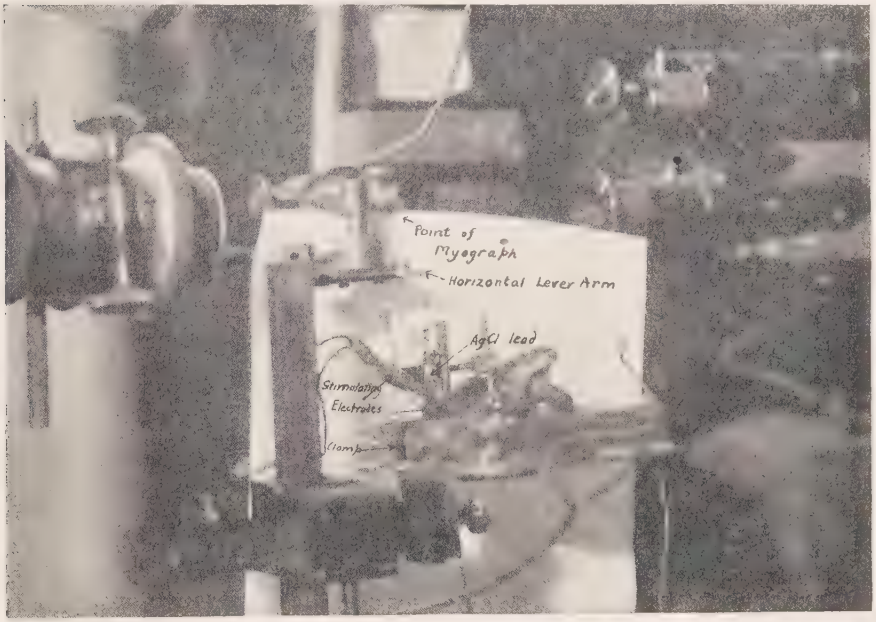


FIG. 9. A "close-up" photograph showing an intact gastrocnemius preparation in position for recording. The stimulating electrodes (S) can be seen on the nerve. The wick of the tendon electrode is resting on the clay plug of the Zn-$ZnSO_4$-NaCl electrode. The proximal silver chloride electrode may be seen inserted into the belly of the muscle through a "window" in the skin. The special clamp fixing the knee-joint to the floor of the moist chamber is also to be observed. The fine point on the needle of the myograph may be clearly seen in the photograph. Ordinarily the whole preparation is enclosed in the moist chamber. (*Amer. Journ. Physiol.*, vol. 75, p. 236, 1925.)

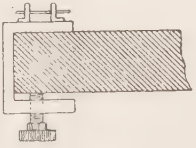


FIG. 10. A diagram of the clamp used to fix the knee-joint of the frog in the moist chamber. The shaded area represents the cork floor of the moist chamber. The needle which is passed through the end of the femur acts as a hinge for the muscle.

the silver pin inserted into the freed part of the muscle 8 to 9 mm. below the tendon. The proximal lead was further protected from the surrounding muscles by covering them with pieces of thin rubber.

For both gastrocnemius and sartorius a light steel hook, passing beneath a tight ligature around the tendon was employed for connecting the muscle with the myograph. The preparation was placed in an electrically heated moist chamber mounted upon a heavy but finely adjustable ratchet-and-pin stand clamped to the experimental table (fig. 6).

D. THE PREPARATION OF THE DECEREBRATE CAT FOR ISOMETRIC RECORDS OF REFLEX MUSCULAR RESPONSES

Accurate study of the reflex responses of mammalian muscle requires the complete denervation of all muscles of the experimental limb, and of all muscles in the fellow limb on the opposite side, except the muscle which is to be used for observation. The procedure for making such a preparation may best be described in Sherrington's (*919*, pp. 115–116) words:

"The animal being deeply narcotized with chloroform and ether, the cranium is exposed by partial eversion of one temporalis from its origin; a trephine hole is made and enlarged with the bone forceps. The animal is then placed supine, the skin reflected in a semicircular flap from the groin, *e.g.*, left, n. cutaneous femoris anterior externus[1] (externus cutaneus) severed just above the inguinal fold, the m. ilio-psoas completely severed well above its insertion, and the n. saphenus and sartorius branches of the n. femoralis (anterio-crural) severed at their origins from that nerve-trunk. In cutting through the ilio-psoas muscle the lumbo-sacral cord and the next following two roots of origin of the sciatic may be met with and severed. The pectineus muscle is then cut completely through, and at its edge, somewhat deep, the n. obturatorius is found emerging from the obturator foramen, and its divisions, both superficial and deep, are severed; n. lumbo-inguinalis (genito-crural) lying close by, alongside the external iliac artery, is also cut through. An incision is then made midway between great trochanter and tuber ischii, and through it the sciatic nerve (peroneal, popliteal, hamstring, and cutaneous branch of n. ischiadicus lying close together) is severed. Enlarging the incision upwards, the n. cutaneous femoris posterior (small sciatic), n. cutaneous clunium inferior and n. pudendus internus above and to the median side of the tuber ischii are found and cut through, as also is the little tenuissimus muscle. Gluteus maximus (both parts) and tensor fasciae femoris are resected completely up from their insertions and the great trochanter thus exposed. Then all the muscles inserted into the trochanter are freely dissected from it and from the capsule of the hip-joint, and in doing this it does not matter if the joint cavity be opened and exposed. Quadratus femoris and gemelli are dissected off from the femur, in doing which it is helpful for the limb to be rotated somewhat inwards. A free incision near the mid-ventral line along the lateral face of the pubes frees the mechanical connection of the adductor group of muscles (left) from the adductor group of the opposite limb. Finally, a loop of thread is placed

[1] In mentioning the nerves, the names here used are those employed by Ellenberger and Baum in the Anatomie d. Hundes: the nomenclature of the muscles is that given by Mivart in the Cat, and by Jayne in his Mammalian Anatomy. The names introduced in brackets are those of the structures in human anatomy with which the parts appear to correspond.

round each carotid artery in the neck and a cannula is inserted in the trachea. The animal is then placed in the prone position again, and while the threads on the carotids are drawn so as to temporarily occlude those arteries, a blunt knife is inserted through an opening in the dura mater and, with the edge of the bony tentorium as a guide, the midbrain is transected at its junction with the hindbrain or through the level of the posterior colliculi. The brain in front of this is broken up or removed through the opened cranial vault. This transaction does not usually endanger the respiratory movements; if it does temporarily do so, artificial respiration is employed through the tracheal cannula. The carotid arteries can usually be freed without danger of haemorrhage in less than five minutes after the decerebration. After decerebration has been performed the chloroform and ether narcosis can be relaxed. Decerebrate rigidity then develops.

"Before examining the reflex, I reflect the denervated skin from the thigh and expose the sartorius, and then take off the whole of that muscle, itself already denervated, right up to its origin, either leaving it reflected or removing it altogether. This allows the rectus femoris portion of quadriceps extensor cruris to be completely seen. The whole pelvic attachment of the rectus femoris is then carefully and fully resected, and a free transverse incision across it below where it merges in the rest of the quadriceps is found not to impair the reactions from this latter, while still further ensuring the exclusion of the rectus femoris itself. In this way a preparation is obtained in which the sole muscle and nerve in the whole limb remaining connected with the spinal cord is the m. vastocrureus and its nerve branch from n. femoralis (anterior crural). Vastocrureus is a single joint muscle. Its blood-supply and mechanical attachments, except for that small part of its upper end which unites with rectus femoris, remain untouched. If care be taken to preserve its exposed surface from cooling and drying, it yields the reactions to be described for several hours after the decerebration. The tonic rigidity characteristic of decerebrate rigidity is not interfered with by any part of the above procedure except that the operation limits the rigidity of course entirely to vastocrureus muscle, and thus in effect wholly to the knee.

"The preparation thus obtained is a unilateral one, in the sense that the vastocrureus of one limb only is isolated. For many observations it is preferable to have the vastocrureus isolated in both limbs. I therefore usually make the preparation a double one by carrying out the above-described procedure on both limbs instead of on one only."

E. THE TECHNIQUE OF CHRONAXIE DETERMINATIONS OF EXCITABLE TISSUES

Since the conception of excitation time or "chronaxie" is of increasing importance to physiologists, especially in view of its application to the phenomena of central nervous conduction now being elucidated to such advantage by Bremer, Lapicque and others, and also in virtue of its great clinical significance as studied in the hands of Bourguignon and Adrian, it is desirable to provide a brief statement of the method employed for chronaxie determinations. The theory of chronaxie and of time constants in general has been discussed briefly in Chapter I. The following description of the apparatus and procedure is taken with some minor alterations from a popular account of Lapicque's investigations recently published in *Nature* (355). The condenser method here described is of course only one

of many, but as it is fraught by fewer difficulties, it is to be commended over other more involved procedures.

Apparatus. For ordinary determinations of chronaxie of the nerves of frogs or mammals, a two- or four-volt accumulator is used as a source of current. This is led into an accurate potential reducer equipped with two hundred equal points of division (see fig. 11). Such *rêducteurs de potentiel* may be obtained from G. Boulitte in Paris.[2] The current is led from the potential reducer by way of a double-contact Morse key to a condenser of variable capacity, so arranged that the condenser is charged when the key is pressed down, and discharged when the key is released (in the accompanying figure the position of the key in space has been reversed). The condenser[3] contains a series of capacities ranging from 0.5 to 0.001 microfarad. In parallel with this condenser is a less accurate condenser having a capacity of two microfarads (fig. 11). This is put into the circuit for the purpose of determining the rheobase, since its time of discharge is so long that it approximates to a constant current. In this way many laborious connections are rendered unnecessary. The wiring and mounting of this apparatus should be so arranged as to minimize self-inductance in all circuits.

The condenser discharges (effected by the double-contact key mentioned above) are led to the tissue through an ingeniously arranged resistance. It will be recalled that the time required for the effective portion of a condenser discharge varies with the external resistance. Unfortunately, the resistance of the nerve fibre or of the muscle substance of a frog varies enormously with the distance between the electrodes, the state of moisture of the preparation, size of fibre, etc., and it would be a difficult task to redetermine a new resistance for each experiment. This difficulty has been overcome by interpolating a shunt of such a low resistance (3000 ohms) as to make the resistance of the tissue excited much greater in comparison and hence negligible. Other resistances are placed in series with the electrodes as shown in figure 11. This resistance (in France *la shunt de Lapicque*), as well as the two-microfarad condenser and the non-polarisable electrodes about to be described, may also be obtained in Paris from Boulitte. The resistance is of graphite so as to have a very low temperature

[2] G. Boulitte, 15 Rue Bobillot, Paris. Price, 900 francs.

[3] Much difficulty has been experienced in obtaining accurately constructed condensers of low and variable capacity at a reasonable price. A *de luxe* instrument may be had from the Cambridge Instrument Company for 30 to 40 pounds. I find also that Beaudouin, 31 Rue Lhomond, Paris, V, is willing to supply, for 700 to 800 francs, a modest but accurate design in two months from receipt of order. J. Carpentier (20 Rue Delambre) supplies, for 1787 francs, a more elaborate instrument of proper range of capacities in three months from receipt of order.

coefficient. When this is used the value R in the equation = CR × 0.37 for the determination of the chronaxie in σ, may be taken as 10,000 ohms, and it is never altered for ordinary determinations. For further details on the external resistance Bourguignon's monograph (pp. 80–82) must be consulted (*190*).

As the rheobase determinations involve constant current of long duration, non-polarisable electrodes must be used. For the nerve a convenient small hard-rubber chamber has been devised by Lapicque containing grooves for kaolin, upon which the nerve may be placed; other non-polarisable electrodes, provided they are not too large, serve quite as well. For the muscle, electrodes of this silver wire, which have previously had deposited upon them by simple electrolysis a coating of silver chloride, are inserted

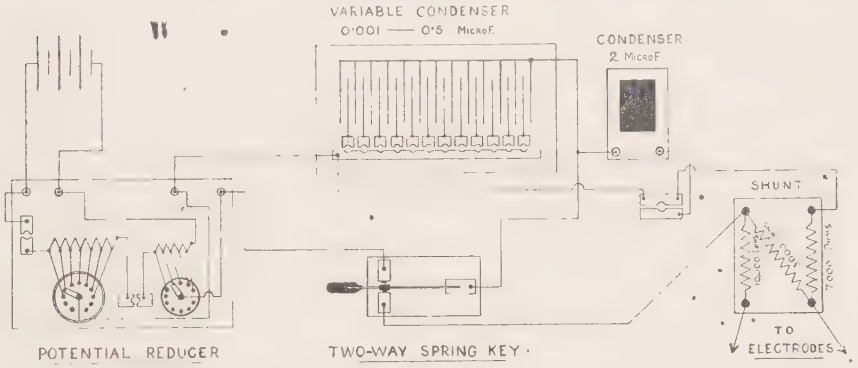


FIG. 11. A diagram of the Lapicque apparatus used for determinations of chronaxie. (*Nature*, vol. 113, March 22, 1924.)

directly into the muscle at convenient distances (0.5 cm. approximate). These may be made very simple by attaching the silver wire to the *positive* pole of a 4-volt accumulator and dipping it in Ringer solution for two minutes, the current being led away from the solution by platinum wire. Such silver chloride electrodes must be renewed daily. Other more complex electrodes have been devised by Bourguignon (*190*) for stimulation through the skin.

Procedure. To determine the chronaxie of the sciatic nerve of the frog, it is preferable to leave the parts so far as possible intact. On a pithed preparation, brain only or cord and brain, the uncut sciatic nerve is exposed and lifted with glass hooks on to the electrodes. Any excess kaolin or moisture between the electrodes is carefully removed and the preparation is allowed to remain quiescent preferably for a half-hour or longer.

To determine the rheobase the two-microfarad condenser is placed in the circuit with the variable condenser (at its highest capacity—1 microfarad) and the least current necessary to excite is then found by gradually increasing the current in the *réducteur de potentiel*. The rheostat on the left of this instrument has twenty points; each of the twenty intervals may be further subdivided into ten by the rheostat on the right, thus giving 200 equal divisions of the potential. A voltmeter is ordinarily used to give the rheobase in absolute units, 0.2 to 0.3 volts being a reasonable value for the nerves of a frog, but it may be much higher. In a single experiment there is frequently considerable variation in the value of the rheobase, but this does not affect the value of the chronaxie. For more accurate determinations of rheobase and chronaxie, as in Bourguignon's (1923) experiments on man, the amperage is also controlled by an additional variable resistance.

To find the chronaxie, the rheobase just determined is doubled by means of the rheostat, or if it is preferred, by the voltmeter. However, with a Boulitte potential reducer it is always safe simply to double the reading of the rheostats. The two-microfarad condenser is withdrawn from the circuit, and the plugs of the variable condenser are arranged for a small capacity, usually 0.02 or 0.05 microfarads. The capacity is then gradually increased until a response is just visible, or if the muscle is attached to a writing lever, until the unloaded lever is just moved. This is the critical capacity from which the chronaxie is calculated by the formula: $\tau = CR \times 0.37$. If the critical capacity proved 0.082 microfarads, and R as usual is 10,000 ohms, we have (C being calculated in farads):

$$\tau = 0.082 \times \frac{10{,}000}{1{,}000{,}000} \times 0.37$$

$$\tau = \frac{0.082}{100} \times 0.37 = 0.000303 \text{ or } 0.3\sigma, \text{ three ten-thousandths of a second}$$

which is normal for the sciatic nerve of the frog when not in connexion with the higher centres. The constant 0.37 is purely empirical (*C. R. Soc. Biol.*, 68, 797), and comes from a comparison of CR with the absolute time determined on the same preparation by means of a ballistic rheotome. For a discussion of this factor see Bourguignon's monograph (p. 10, and Vogel (*1004*)).

When the chronaxie of a muscle is determined, silver chloride non-polarisable electrodes are used as explained above. They are inserted just into the muscle substance separated by 0.5 cm. or less, and the index of adequacy of stimulation is not the complete contraction of the muscle but rather the first visible twitch at the cathode. Otherwise there is a great spread of

current and the chronaxie appears much larger than it is (Davis, *224*). Theoretically, the most satisfactory electrodes for determining the chronaxie of muscle are the sodium chloride pore electrodes used with success by Davis (*223*), which stimulate but a single muscle fibre (observed under the microscope).

Attention may be directed to a most useful account of the theory, technique and clinical significance of chronaxie determinations, which was published in 1923[4] by Percival Bailey. The reader may profitably consult this for further details.

[4] Bailey, P. (1923) "Recent developments in electrodiagnosis." Arch. Neurol. & Psychiat., vol. 9, pp. 436-449.

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